Evaluation of cholesterol guidelines in general practice

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Where is the wisdom we have lost in knowledge?
Where is the knowledge we have lost in information?
T.S. Eliot

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Chapter 1

General introduction

Abstract

The relevance of national guidelines on cholesterol management and the rationale for their evaluation in practice are described. The cholesterol guidelines were developed through a consensus procedure and based as much as possible on published scientific data. The evidence available during the development of the guidelines is described in the first part of the introduction, summarising the state of the art at the start of this research project. The conclusions from this available evidence are reported together with the description of the guidelines themselves. The second part of this chapter describes a research model for the evaluation of practice guidelines. The research model is divided in two main components; the evaluation of the feasibility of the guidelines, and the evaluation of its scientific validity. Finally, an outline is given of both how the research model for the evaluation of practice guidelines was translated into the research questions and how this book is organised.

The first part of this chapter was published as: Weijden T van der. Wetenschappelijke achtergronden bij de NHG-standaard Cholesterol. Een literatuuroverzicht. [Scientific background of the DCGP standard on Cholesterol. A literature review.] Huisarts Wet 1992;35:90-6.

Introduction

About a quarter of the yearly mortality in the Netherlands is caused by coronary heart disease (CHD). This is more than half of all cardiovascular disease mortality[1]. Hypercholesterolaemia, together with cigarette smoking and hypertension, are thought to be the most important risk factors for the development of CHD. Therefore, screening for and reduction of cholesterol levels in the population have been important topics for care and research for decades. Specific developments in the 1980s had their impact on cholesterol screening activities. Some important cholesterol intervention studies reported a positive effect on CHD morbidity and mortality, new cholesterol-lowering drugs (HMG-coA-synthesis reductase inhibitors) were introduced as well as desktop blood-testing devices for cholesterol testing. These developments[2] prompted the Dutch College of General Practitioners (DCGP) to establish a well-balanced[3] standard for hypercholesterolaemia, which was published in November 1991 (see appendix 1). Cautiousness in screening and drug therapy characterises these practice guidelines.

The standard for cholesterol was developed through a consensus procedure. Although attempts were made to found the guidelines on the scientific facts published in the medical literature, several factors did influence the interpretation of the medical evidence[4]. It is not always clear how far guidelines for general practitioners can be based upon the information on efficacy of cholesterol-lowering interventions in the scientific literature. Setting a standard requires compromising during the consensus meetings. The question is whether the cholesterol guidelines are sufficiently evidence-based. Moreover, does the publication of these guidelines really have an effect in daily practice? Do GPs adhere to the guidelines, and are they feasible? The Dutch College of General Practitioners has been publishing standards only since 1989 so there is not much expertise on the implementation of practice guidelines yet.

The evidence that was available during the development of the guidelines, the scientific background for the cholesterol standard, is described in the first part of this chapter, followed by the description of the guidelines themselves. In the second part of this chapter a research model for evaluation of practice guidelines is described and translated into the research questions investigated in this thesis. Finally, the structure of the book is outlined.

Background

Classification of serum cholesterol

Hypercholesterolaemia, and particularly an increase in low density lipoprotein (LDL) level, has long been recognised as an important risk factor for coronary heart disease (CHD)[5] [6]. The clinical relevance of the high density lipoproteins (HDL) and triglycerides is still under discussion[7]. Hypercholesterolaemia is not an uncommon risk factor among the Dutch population. Only one-third of the adult population (20-60 years) has a serum

cholesterol level lower than 5.0 mmol/l, and nearly one-fifth has a level higher than 6.4 mmol/l[8]. The serum cholesterol level increases with age. A sharp increase between 20 and 40 was shown for men, while this occurred for women after the age of 45. One person in 500 is known to have a very high serum cholesterol level (8 to 14 mmol/l) due to the heterozygote form of Familiar Hypercholesterolaemia[9].

The relation between serum cholesterol and CHD incidence has been investigated in 360,000 men aged 35 to 57 years[10]. After 6 years of follow-up it became clear that there is a continuous positive relation between serum cholesterol and CHD mortality. A clear cut-off point above which the CHD-mortality strongly increased was not found. The European Atherosclerosis Society arbitrarily set cut-off points (5.2 and 6.5 mmol/l), based on these data[11]. The differences in mean serum cholesterol values between populations further confounds the lack of transparency of the definition of normality. The mean serum cholesterol of the adult population is 5.8 mmol/l in the Netherlands, 5.4 mmol/l in the US, and 4.5 mmol/l in Japan[12]. Compared to Japan, the western world has a CHD incidence more than twice as high[13]. However, it is not clear what a safe cut-off point is for normal, healthy serum cholesterol levels[7].

Predictive value

The predictive value of hypercholesterolaemia regarding the risk of developing CHD is low. Cholesterol distribution curves of middle-aged men that either do or do not develop CHD in a period of 15 years show a great deal of overlap[6 14 15]. Over 60% of CHD occurs in persons with a cholesterol level lower than 6.4 mmol/l. The mean serum cholesterol of patients with CHD is 6.3 mmol/l, and of persons without CHD 5.7 mmol/l[16]. The relation between hypercholesterolaemia and CHD is far more dramatic for persons suffering from Familial Hypercholesterolaemia. Half of the men and 15% of the women with the heterozygote form have at least one myocardial infarction before the age of 60[17].

The gender factor. The CHD incidence is about twice as large for men than for women, and is low especially for women in the fertile period[18-20]. The type of relationship between serum cholesterol and CHD is not equal either for men and women. The likelihood of a 45-year-old person developing CHD in 6 years time, given that the serum cholesterol level is 8.0 mmol/l and no other risk factors exist, is nearly four times higher for men than for women (5.8 against 1.6%)[21]. The relation between serum cholesterol and CHD incidence seems less consistent for women than for men[22], as is further illustrated by table 1. For men, the risk on CHD increases continuously with the rise in serum cholesterol in all age categories. This curvilinear relation exists also, although less prominently, for women aged 40-49 years. For women aged 30-39 years there hardly seems to be a relationship and for women aged 50-59 years there is a J-shaped relation. A prospective study on women aged 60 years and over also showed a J-shaped relationship[23]. In a study of men and women aged 49-82 years a low LDL level was related to a low CHD incidence. But the women with a low LDL level showed a higher cerebrovascular disease incidence than the women with a high LDL level[24].

ctor. In the Seven Countries Study, the MRFIT Study and the Framingham
trength of the relation between serum cholesterol and CHD mortality decreased
7. Below the age of 50 serum cholesterol seems directly related to CHD and
ity. There is controversy on the strength of this relationship in the elderly. It
sappear between the age of 50 and 70 years[28-30]. Nevertheless, in other studies
esterol appeared, in contrast to smoking and hypertension, to be an independent
for CHD mortality for men and women aged 65 and over[31], or for elderly
y[32].

OLUTE RISK OF CHD IN 24 YEARS PER 1000 MEN OR WOMEN, RELATED TO THE SERUM CHOLESTEROL
NDARDISED FOR AGE[33].

30-39 yrs		40-49 yrs		50-59 yrs	
♂	♀	♂	♀	♂	♀
82	60	271	97	438	386
136	99	292	89	432	307
252	43	344	135	588	259
286	67	360	165	520	292
382	69	579	297	817	364

holesterol-lowering interventions

olesterol-lowering diet the serum cholesterol level can be reduced by 8 to 15
. In controlled intervention studies a reduction of 13% is usually reached; in the
ituation a reduction of 9% can be reached, given that good quality support is
[38] and sustained[39]. While the classical cholesterol-lowering drugs could establish
rol reduction of about 10%[40 41], the new generation drugs, the HMG-CoA-
nhibitors, seem more powerful in their cholesterol-lowering ability. Simvastatin
an reduction of 27% (20 mg daily dose) to 33% (40 mg)[42-44].

rgest randomised placebo-controlled intervention studies on cholesterol-lowering
the WHO Cooperative Trial on Primary Prevention of Ischaemic Heart Disease
al)[45 46], the Lipid Research Clinics Coronary Primary Prevention Trial (LRC
d the Helsinki Heart Study (HH study)[48]. These trials are aimed at middle-aged
ut further (highly) elevated risks for CHD. The follow-up period varied between
ears, and the mean baseline cholesterol levels ranged from 6.4 till 7.5 mmol/l.
ention was 1.6 gram clofibrate per day in the WHO trial, diet and 24 gram
nine per day in the LRC trial, and 1200 mg gemfibrozil per day in the HH
results are summarised in table 2.

ute risk of CHD was 1.5% lower in the intervention than in the control groups.
ever, did not result in a decrease in total mortality, which was in two studies
r in the intervention than in the control group. A relatively high mortality on
l violence (accidents, murder, suicide) was reported in the intervention groups.
omenon was also described by Muldoon in a meta-analysis of six intervention

studies with a total study population of 25,000 men[49]: CHD mortality was 1.35% in the intervention groups and 1.59% in the control groups (odds ratio 0.85), whereas the percentages were 0.53% and 0.30% for mortality from violent deaths in the intervention and control groups respectively (odds ratio 1.76). The interventions consisted of a cholesterol-lowering diet in two studies and of different cholesterol-lowering drugs in the four other studies. The high mortality due to violence could therefore not be clarified by side-effects of a certain cholesterol-lowering drug.

TABLE 2. RESULTS OF THREE INTERVENTION STUDIES. NUMBERS PER 1000 MEN.

	non-fatal MI		CHD mortality		CHD total		total mortality	
	I-group	C-group	I-group	C-group	I-group	C-group	I-group	C-gr.
WHO	37	48	10	9	47	58	36	24
LRC	68	83	16	20	81	98	36	37
HH	22	35	5	6	27	41	22	21

It is interesting to interpret the results of these trials in another way, namely by considering the number of men that do not develop CHD[50]. In the HH study 973 out of 1,000 participants in the intervention group, and 959 out of 1,000 in the control group, remained free of CHD. This means that the chance to remain free of CHD during a period of five years improved from 96% to a little over 97%. Fourteen out of one-thousand treated men did profit from the intervention. There was no profit for 986 men: the 959 that had remained CHD-free and the 27 men that developed CHD despite the use of gemfibrozil.

Implications for screening

General screening of the Dutch population is not to be recommended for the following reasons: although the prevalence of hypercholesterolaemia is high, it has a low predictive value regarding CHD; the accuracy of one measurement of the serum cholesterol is low[51] [52]; the safety of the long-term effects of the new cholesterol-lowering drugs has not been established yet; the cost-effectiveness ratio of a national screening programme seems negative[41] [53]. Screening persons with Familiar Hypercholesterolaemia, on the other hand, has the highest priority, but this patient group is too small to justify national screening[54]. An effective screening strategy is not available (yet).

The effect of intervention on population level was compared with selectively screening the persons with high risk for CHD only[55]. If health promotion can reduce the mean serum cholesterol on population level by 4%, the number of cigarette smokers by 15%, and the mean diastolic blood pressure by 3%, this would bring about a reduction in the CHD mortality of 18%. On the other hand, if the mean serum cholesterol in a high risk group only were reduced by 34%, the number of smokers by 20%, and the mean blood pressure to a level of 90 mmHg, this would reduce the CHD mortality by 2% to 9%. Thus, the effect of the population strategy seems to be about twice as high as the effect of the

selective high-risk strategy, which was affirmed in another study[56]. It was calculated o Framingham data that men aged 40-60 years would profit most from cholesterol-lowerin intervention[57]. The effect for women below 40 and for men and women above 60 is le clear, and therefore a selective high-risk strategy is much needed for these groups.

The selective high-risk strategy

The DCGP standard on Cholesterol recommends passive selective screening (case findin based on the individual's risk profile for coronary heart disease. This was grounded on tl fact that a combination of risk factors multiplies the risk. There is not much point treating hypertension if the same patient's hypercholesterolaemia remains untreated The risk to develop CHD in 8 years time is 4 per 1,000 for a 35-year-old man with serum cholesterol level of 8.7 mmol/l. If the patient also suffers from diabetes mellitus, t risk increases to 23 per 1,000, and to 35 per 1,000 if he also smokes cigarettes and h hypertension. Although it is hard to assess the independent risk of the different ri factors, an indication can be given of the relative impact of the different risk factors. 10% reduction of the serum cholesterol level and of the diastolic blood pressure shou result in a reduction in total mortality of 4.4% and 14.1% respectively. Reducing smoki by 10 cigarettes a day should lead to a 20% reduction in total mortality. The larger imp of smoking and blood pressure can be explained by the fact that these risk factors are al related to other important diseases, such as lung cancer and cerebrovascular accidents This way of ranking the three main risk factors was affirmed in the Framingham Stud and a study executed in the general practice setting[60].

Although most studies on cost-effectiveness are restricted to cholesterol-loweri drugs[61-64], there are two cost-effectiveness analyses in which different screening strateg were compared. They advocate cautiousness in the selective high risk strategy while population screening seemed to be more effective, and to reserve cholesterol-loweri drugs for patients with a very high risk of CHD, such as patients with Familiar Hypercl lesterolaemia[65 66].

Translation of the evidence into guidelines

Evidence from the review of the scientific research leads to the following conclusions. ' prevalence of hypercholesterolaemia is high among the Dutch adult population. ' classification of borderline and elevated serum cholesterol was based on arbitrary cut- points, that are not validated for other persons than middle-aged men. The predictive va of hypercholesterolaemia appeared low, especially for women and the elderly, with exception of patients with Familiar Hypercholesterolaemia. Trials on cholesterol-lower interventions were mostly executed among white middle-aged men[67 68]. It is not c whether the results of these studies may be extrapolated to other subpopulations[69]. ' results of the intervention studies seemed disappointing, considering the modest abso risk reduction in the intervention compared to the control groups. Perhaps the length of

follow-up periods was too short, especially to measure the effect on total mortality[70]. The atherosclerotic process might have been too advanced to be influenced by the cholesterol-lowering interventions. The relatively high non-coronary mortality could not be clarified. Was it coincidence, or caused by the more active lifestyle which may result from prevention of early symptoms of coronary heart disease, such as tiredness and angina[71]? Was it due to deterioration of the cell membrane composition[72], or was aggressive behaviour related to low serum cholesterol[73]? No signs were found for a specific effect of suddenly lowering the patient's serum cholesterol which had been high for years[74]. To justify a screening strategy a high quality cost-effective analysis is needed, analysing different screening and intervention strategies in general practice populations, using general practice outcomes, and calculating both positive and negative effects of screening.

These conclusions were the starting point for the consensus meetings of the DCGP standard working group on cholesterol. The national guideline for Cholesterol (see Table 3 and appendix 1) eventually recommended a selective case finding strategy, repetition of testing to confirm the diagnosis hypercholesterolaemia, and cautiousness in drug therapy, especially for women in the fertile period.

TABLE 3. THE DCGP STANDARD ON CHOLESTEROL: KEY RECOMMENDATIONS.

Case finding:
Selective case finding; the targeting of cholesterol testing to those individual patients, that for whatever reason attend the practice-office, and that are known to have an increased individual risk profile for coronary heart disease. Increased risk: men and women, 18-65 yrs, with one of the following risk factors; signs of Familial Hypercholesterolaemia (xanthoma, xanthelasmata/arcus senilis before the age of 40), CHD in patient history, CHD in sibling or parent while younger than 60, hypertension, diabetes mellitus, familial hyperlipidaemia in the family.
Patients whose only risk factor is smoking are advised to cease smoking first.

Diagnosis:
Diagnosis of hypercholesterolaemia: the mean of 3 cholesterol tests higher than 6.5 mmol/l, determined in a period of 6 weeks. Determination of HDL and triglycerides only in case cholesterol-lowering drugs are being considered.

Management:
The patient should be referred in case of Familial Hypercholesterolaemia.

< 6.5 mmol/l:	General advice about low-fat diet
> 10.0:	Consultation of an internist
6.5-10.0:	Prescribe diet therapy, with support, for 6 months. Referral to dietician if unsuccessful.

Consider cholesterol-lowering drugs after 6 or 12 months of diet therapy if (with the remark that women without Familial Hypercholesterolaemia do not seem to profit from drug therapy):
serum cholesterol 6.5-7.9 mmol/l and $\geq$ 2 risk factors (as defined under case finding)
serum cholesterol 8.0-10.0 mmol/l and $\geq$ 1 risk factor(s)
Target level for serum cholesterol: 6.5 mmol/l

The research model

When an intervention seems to be effective according to the literature, what are then the implications for clinical practice? In particular, how strong are any inferences about

screening or treatment, and does the strength of inference differ between subgroups of patients? Being able to answer these questions will be crucial in the process of going from the available evidence to specific health care recommendations and clinical practice. Tugwell et al. described in 1985 a measurement iterative loop for the critical appraisal of need, benefits and costs of health interventions[75]. Efficacy and effectiveness of health care interventions are important concepts in this matter. Efficacy asks the question "Can it work?". It is defined as the extent to which a health intervention does more good than harm to patients under optimal trial conditions, that is the patients are diagnosed correctly, appropriately cared for and fully compliant with recommendations for treatment. Effectiveness, or community effectiveness according to Tugwell, asks whether the intervention will work when applied in the community. Community effectiveness is defined as "efficacy x diagnostic accuracy x health provider compliance x patient compliance x coverage". In the process of evaluating community effectiveness and developing or updating recommendations, feasibility features need to be given attention in order to have insight into health provider and patient compliance as well as coverage. Assessments of community effectiveness, cost-effectiveness and feasibility should be regarded as an indivisible, cyclical process and have to be integrated to make recommendations for updating and/or implementation of health care recommendations.

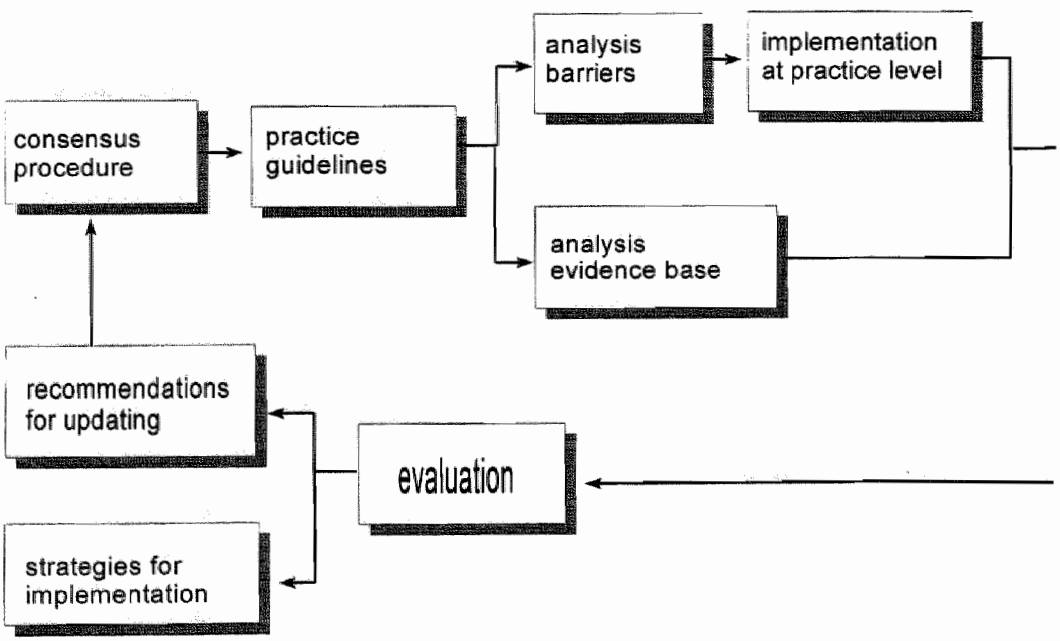

FIGURE 1. THE RESEARCH MODEL FOR EVALUATION OF PRACTICE GUIDELINES.

Based on these considerations a research model (Figure 1) was constructed for this project. The evaluation of the feasibility of the guidelines on the one hand and the evaluation of the evidence base for the guidelines on the other are situated as parallel projects in the research model. By means of a standardised *consensus procedure* scientific evidence and clinical expertise are translated into *practice guidelines* (procedure of the Dutch College of GPs). For the assessment of the feasibility of the guidelines the *usual care has to be investigated*, to assess the discrepancy between the guidelines and the reality of daily practice. Subsequently, the barriers to working according to the guidelines have to be identified, in order to develop specific implementation strategies. These implementation strategies have to be tested for (conditions for) feasibility in some general practices (*implementation at practice level*). The effectiveness of the preventive guidelines has to be checked for its evidence base in a parallel study by *analysis of the evidence base*. All these steps may result in recommendations for updating of the guidelines and/or strategies for implementation.

It is known that health care provider adherence to a guideline is not a logical consequence of the dissemination of this guideline[76]. Many of the existing practice guidelines do not even reach the GPs[77] [78]. Physicians' compliance with preventive medicine is not very high[79], and they often overestimate their preventive services[80]. Evaluation studies on dissemination and implementation of cholesterol guidelines have shown that, in order to influence medical practice, guidelines on cholesterol need extensive support from educational and quality improvement activities[81] [82]. Different problems arise in the prevention of coronary heart disease, such as lack of motivation, that need to be overcome before GPs will comply to practice guidelines[83-86]. The dissemination and implementation of guidelines therefore seems to be a complex process, in which numerous factors play their part. In implementing guidelines, it is recommended to gain insight into barriers to working according to certain guidelines, to develop specific implementation strategies and to assess whether these strategies are effective[87]. In this thesis the feasibility and applicability of the cholesterol guidelines in the general practice setting will be questioned. It might be concluded in the evaluation of the feasibility that either specific implementation strategies are necessary to improve the adherence to the guideline, or that the content of the guideline needs to be changed to ensure that GPs at least demonstrate good adherence to the key-part of the guidelines.

The scientific value of the evidence deserves continuous attention because the state of the art is continuously developing. The need for evidence on preventive guidelines requires, due to the medical, economic, and social implications, attention both from the area of effectiveness as well as the cost-effectiveness of the preventive procedure in medical practice[88]. Therefore, scientific evidence has to be sought on both effectiveness and efficiency of serum cholesterol diagnosis and therapy in the general practice setting. In so-called 'primary prevention' (intervening in persons that do not show symptoms of the disease that one is targeting on) different processes need to be analysed, namely the predictive value of hypercholesterolaemia, the diagnostic accuracy of the screening-

procedures, and the capability of the intervention to improve the patient's health (Figure 2). Do asymptomatic persons with an increased risk of CHD show a significantly better response to treatment than those who present themselves with CHD symptoms? Only if this information is available can the cost-effectiveness of the preventive intervention be analysed. In this thesis the evidence base on effectiveness and cost-effectiveness of cholesterol-lowering interventions in general practice will be questioned.

FIGURE 2. CAUSAL PATHWAY FOR PREVENTIVE INTERVENTIONS IN ASYMPTOMATIC INDIVIDUALS*.

	early detection ↓		treatment intervention ↓		predictive value ↓	
asymptomatic individuals	->	identification of the risk	->	reducing the risk	->	favourable outcome

* modified from: Battista RN, Fletcher SW. Making recommendations on preventive practices: methodological issues. In Battista RN, Lawrence RS, Eds. Implementing preventive services. New York: Oxford University Press 1988:53-67.

Study questions

The evaluation of the feasibility of the guidelines and the evaluation of the evidence base for the guidelines are situated as parallel projects in the research model. The following study questions were formulated on the basis of this model:

I *Are the guidelines feasible and applicable in practice?*

1.1 What is the usual care in Dutch general practices regarding screening and management of hypercholesterolaemia like? Does discrepancy exist between current practice and the DCGP standard on Cholesterol?

1.2 If a discrepancy does exist between current practice and the guidelines, what are the barriers for adherence to the guideline? Which strategies can be developed to optimise the implementation of the guidelines?

1.3 Are the guidelines used after intensive implementation strategies?

II *What is the evidence base of the guidelines?*

2.1 What is the present state of the scientific evidence on the effectiveness of cholesterol lowering on CHD morbidity, non-CHD morbidity, and CHD mortality and total mortality? Is the evidence generalisable to the general practice setting?

2.2 What is the present state of the scientific evidence on the cost-effectiveness of different cholesterol-screening strategies in general practice?

Structure of this book

Chapters 2, 3 and 4 report on various investigations of usual care in the field of cholesterol diagnosis and therapy in general practice. In chapter 2 cholesterol management in Dutch general practice is reported in the years before publication of the DCGP guideline, in chapter 3 case finding performance is reported in the years around publication of the guidelines, and in chapter 4 trends in cholesterol testing are described over the period 1984 till 1992. The feasibility of the guidelines is investigated in chapters 5 and 6. A programme for improvement was developed in a systematic way, based on possible barriers to change (appendix 2). In chapters 5 and 6 the feasibility of cholesterol guidelines in general practice is evaluated by applying the programme for improvement in 10 general practices. The effect of the programme for improvement on actual performance is presented in chapter 5. The influence of the programme for improvement on the GPs' knowledge of and attitude towards the cholesterol guidelines is described in chapter 6, as well as the barriers to change experienced by this group of GPs. The scientific value of the cholesterol guidelines in general practice is reported in chapter 7 in the format of a systematic review of randomised controlled trials on cholesterol-lowering interventions. Chapter 8 gives a systematic review of studies on cost-effectiveness of cholesterol-lowering interventions. In chapter 9, the discussion, the strengths and limitations of the project are discussed, recommendations for updating and implementation of the cholesterol guidelines are given, including recommendations for further research in this field.

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Investigation of usual care

Chapters 2, 3 and 4 report on various investigations of usual care in the field of cholesterol diagnosis and therapy in general practice. In chapter 2 cholesterol management in Dutch general practice is reported in the years before publication of the cholesterol guidelines of the Dutch College of General Practitioners, in chapter 3 case finding performance is reported in the years around publication of the guidelines, and in chapter 4 trends in cholesterol testing are described over the period 1984 till 1992.

Chapter 2

Cholesterol management in Dutch general practice. A comparison with national guidelines.

Abstract

Objective - To examine cholesterol diagnosis and treatment by Dutch general practitioners (GPs) in the period before publication of national guidelines, in order to develop implementation strategies based on discrepancies found between daily practice and the guidelines.
Design - Data of the 'Dutch National Survey of General Practice', in which GPs were involved in extensive consultation registration, were used. Patients were included for analysis if serum cholesterol, or the ICPC-code lipid metabolism disorder, or cholesterol-lowering treatment was registered.
Setting - General practice.
Participants - 161 GPs, 177 practice-nurses.
Outcome measures - Reasons for consultation, diagnoses, therapy, inter-doctor variation.
Results - The main discrepancies between daily practice and the guidelines concerned indications for cholesterol measurement, repeated measurements to diagnose hypercholesterolaemia, and attention for diet advice. Remarkable inter-doctor variation in diagnosis, and less so in treatment, was also found.
Conclusion - The inter-doctor variation justifies the publication of the standard guidelines. Implementation strategies should aim at indications for cholesterol testing, repeating measurements for diagnosis, and advice on diet.

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Introduction

The publishing of the results of important cholesterol intervention studies in the 1980s[1,2] stimulated consensus meetings in various countries. In addition there are developments such as the introduction of new cholesterol-lowering medication and the portable capillary blood-testing device for cholesterol measurement. These developments[3] prompted the Dutch College of General Practitioners to set a well-balanced[4] standard for hypercholesterolaemia, which was published in November 1991[5] (appendix 1). Meanwhile the cholesterol topic is still controversial[6,7,8], and there is no consensus in the literature as to which screening strategy is to be preferred in general practice[9].

Not much is known about the usual cholesterol care by Dutch GPs. A description of the usual cholesterol care, including the inter-doctor variation, in the period prior to publication of the guidelines, serves various purposes; it may show problems with the feasibility of the guidelines. It might also increase insight into deficiencies in the provided care and points of attention for implementation of the standard[10].

In this study we present findings on the following questions:

1. Who were the patients, in the period prior to publication of the guidelines, whose serum cholesterol was tested by the GP, and how was hypercholesterolaemia diagnosed? How was the inter-doctor variation?
2. How were patients with hypercholesterolaemia treated by their GP in the period prior to publication of the guidelines? How was the inter-doctor variation?

Methods

Data of the 'Dutch National Survey of General Practice'[11] were used to answer these questions. In this survey, 161 GPs and 177 practice-nurses, working in 103 Dutch practices serving 335,000 patients, registered all doctor-patient or nurse-patient contacts during a period of three months. The survey, lasting from April 1987 to March 1988, consisted of four consecutive registration periods of three months each to account for seasonal influences. Selection of participating GPs was based on a stratified (according to region, urbanization, and distance to a general hospital) random sample.

Data recorded include patient characteristics, characteristics of the consultation, reason for consultation, diagnosis, and interventions (diagnostic tests, non-drug and drug treatment, referral). Different health problems presented in one consultation were registered separately. Each health problem contained a maximum of three reasons for consultation, one diagnosis and two differential diagnoses. Reasons for consultation and diagnoses were coded in ICPC codes. The GPs could mark on their registration form that they requested a lipid spectrum including total cholesterol and/or triglycerides and/or lipoproteins and/or free fatty acids. Checking the laboratory-forms showed that all lipid spectrum applications included at least total cholesterol. A distinction was made between patients who consulted their GP for the first time in relation to reasons that resulted in a request for a lipid spectrum ('new']

tients), and those who had already consulted their GP before the registration-period, with problems related to cholesterol diagnosis or intervention ('known' patients).

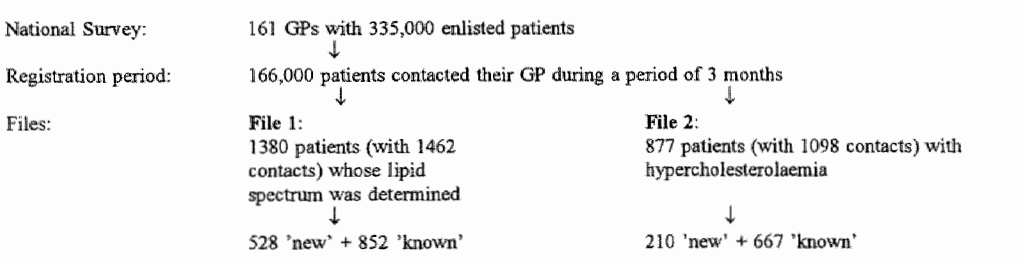
To answer the first question all contacts in which a lipid spectrum was determined were selected (file 1). File 1 consists of 1380 patients (1462 contacts). Regarding question 2 a second, separate selection was made consisting of:

- all patients of file 1 with hypercholesterolaemia (the norm for hypercholesterolaemia was not standardised for the laboratories involved. It varied from 6.0 to 7.0 mmol/l.);
- all patients in whom the ICPC-code lipid metabolism disorder (T93) was registered as reason for consultation or diagnosis;
- all patients for whom a cholesterol-lowering drug was prescribed.

This file 2 includes 877 patients (1098 contacts) with hypercholesterolaemia. The structure of the files is summarised in Figure 1.

The amount of inter-doctor variation was studied by means of the coefficient of variation (CV)[12]. The CV (dividing the standard deviation by the mean) is a measure for relative variability. To explore the determinants of this variation, multiple linear regression analysis was used. GPs in file 2 who had less than three patient contacts on the subject (n=59) were excluded from this analysis. Correlation coefficients were calculated to explore substitution between different kinds of therapy.

FIGURE 1. THE STRUCTURE OF THE TWO CHOLESTEROL FILES.



Results

Diagnostics

A cholesterol test was ordered in 0.8% of all the patients (1380/166,000) who had visited their GP during the registration period of three months. The patients for whom a lipid spectrum was requested were on average 50 years old. Half the patients were between 45 and 64 years old. The sex distribution of the patients involved was almost symmetrical. According to the guidelines, the age-criteria for screening of cholesterol are between 18 and 65 years. Of the 'new' patients 21.5% did not meet these age criteria (Figure 2). This percentage was considerably higher for older women (25.4%) than for older men (17.4%).

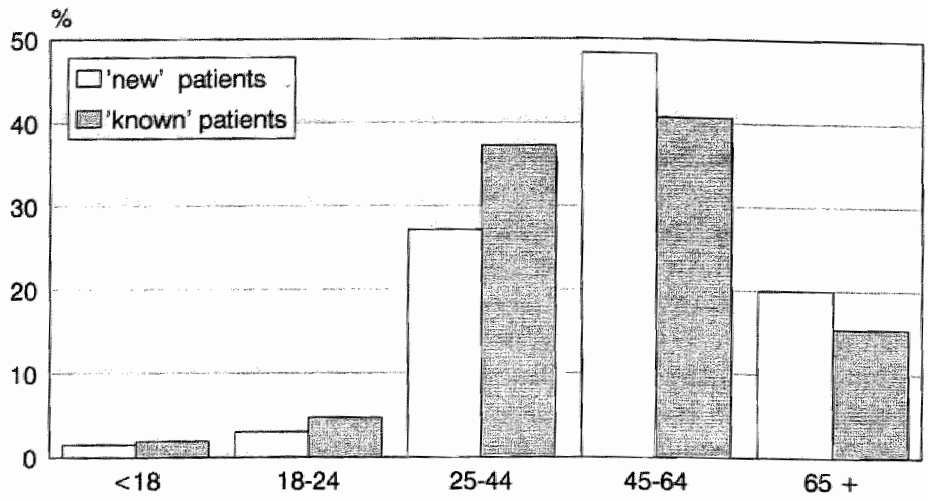


FIGURE 2. AGE-DISTRIBUTION OF 'NEW' AND 'KNOWN' PATIENTS. PERCENTAGES.

Table IA lists the 10 reasons for consultation most frequently presented by the patients.

TABLE 1. TOP 10 REASONS FOR CONSULTATION AND TOP 10 DIAGNOSES FOR PATIENTS IN WHOM SERUM CHOLESTEROL W/ TESTED (PERCENTAGES).

	'new' patients (n=528)		'known' patients (n = 85
A. Reasons for consultation			
1. General weakness/tiredness	18.6	Blood pressure measurement	2(
2. Symptoms thorax/rib	8.1	Blood test (metabolism)	8
3. Blood pressure measurement	6.6	General weakness/tiredness	(
4. Complete medical examination	6.3	Complete medical examination	
5. Blood test (metabolism)	5.5	Partial medical examination (metabolism)	
6. Headache (excl.sinus)	4.5	Lipid metabolism disorder	
7. Symptoms leg/thigh	4.0	Results test/procedures	
8. Vertigo/dizziness	3.6	Observation/health education/diet (metabolism)	
9. Palpitations/awareness of heartbeats	3.2	Generalised abdominal pain/cramps	
10. Partial medical exam (metabolism)	3.2	Symptoms leg/thigh	
B. Top-10 diagnoses			
1. Uncomplicated hypertension	6.3	Uncomplicated hypertension	2
2. No disease	6.1	Lipid metabolism disorder	1
3. Lipid metabolism disorder	5.5	Complete medical examination	
4. Neurasthenia	4.9	No disease	
5. General weakness/tiredness	4.4	Diabetes mellitus	
6. Complete medical examination	3.8	No diagnosis	
7. Feeling anxious/nervous/inadequate	3.0	Feeling anxious/nervous/inadequate	
8. Acute stress/situational disturbance	2.1	Neurasthenia	
9. Diabetes mellitus	2.1	Depressive disorder	
10. Angina pectoris	1.7	General weakness/tiredness	

For 'new' patients a lipid spectrum was most frequently - 33.9% of all reasons - indicated on non-specific symptoms such as general weakness/tiredness, headache, vertigo/dizziness, palpitations/awareness of heartbeats. Contacts concerning health check-ups (complete and partial medical examination) accounted for 9.5% of all the reasons for consultations. Of the 'known' patients the non-specific indications (general weakness/tiredness and generalized abdominal pain/cramps) were of lesser magnitude (8.4% of all the reasons for consultations). Cholesterol measurements in this group of patients were more often indicated in control of hypertension (blood pressure measurement), lipid metabolism disorder, or health-check-ups.

Table 1B lists the top 10 diagnoses of 'new' and 'known' patients with the reasons for consultation as mentioned in Table 1A. In the first group hypertension, no disease, and lipid metabolism disorder were most common, but did not occur much more than the other diagnoses. The other diagnoses, except diabetes mellitus and angina pectoris, were mainly psychiatric in nature. In the group of 'known' patients hypertension and lipid metabolism disorder were by far (40.6%) the most common diagnoses.

In 5% of the patients serum cholesterol was determined by more than one measurement during the registration period of three months. The number of requests for lipid spectra varied between the GPs (Table 2). Half of the GPs requested 1 to 5 measurements per 1000 patients over the period of three months. The GP with the highest number of measurements requested 27.4 per 1000 enlisted patients. The average was 4.1 lipid spectra per 1000, with a standard deviation of 3.5 (CV = 0.85).

TABLE 2. INTER-DOCTOR VARIATION IN NUMBER OF REQUESTS OF LIPID SPECTRA PER 1000 PATIENTS. PERCENTAGE GPS TO NUMBER OF REQUESTS PER 1000 PATIENTS.

	< 1.0	1.0-4.9	5.0-9.9	10.0-14.9	≥ 15.0
% GPs	16	52	27	5	0.6

Doctor and practice characteristics were explored to explain this inter-doctor variation (Table 3). GPs working solo requested cholesterol tests more often, while GPs with large patient lists requested less often.

Therapy

The GPs advised and/or informed 42% of the patients; 39% of 'known' and 51% of 'new' patients. Diet therapy was given to 15% of 'known' and 13% of 'new' patients. The GPs referred three percent of the patients to a dietician. Cholesterol-lowering drugs were prescribed to 25% of 'known' and 1% of 'new' patients. Table 4 gives an overview of prescribed drugs. Bile acid binders were prescribed mostly, followed by nicotinic acid, and fibrates. Over 10% of women under the age of 50 were prescribed lipid lowering drugs.

OF CHOLESTEROL REQUESTS EXPLAINED BY GP AND PRACTICE

Standardised regression coefficients (beta). Beta	significance
-0.004	0.96
-0.017	0.89
0.023	0.79
0.022	0.83
-0.240	0.01
0.091	0.32
0.087	0.31
0.226	0.01

out in this analysis

e for the prescription of fibrates (CV = 3.28). The
of nicotinic acid (CV = 2.86) and in referral to
ion in therapy could not be explained by any of th
ɔned in Table 3. No correlation was found betwee
gree of prescribing cholesterol-lowering drugs
s.

AND POSTMENOPAUSAL (AGE CRITERION 50 YEARS) (PERCENTAG

♀ ≤ 50 n=122	♀ > 50 n=285	total n=8
68	44	57
1	7	5
9	16	14
3	13	9
1	-	0.1
7	17	13
16	16	13

rs[13-16] and medical chart audits[17-19] were conducted
ɔlesterolaemia by GPs. It is quite possible that th
ially desirable information or expose only part
ısual care based on intensive consultation registrat

little insight into the anamnestic part of the consu
l Hypercholesterolaemia for which no specific IC

code exists. Cholesterol screening is supposed to be executed in an anticipatory way, by case finding. The trigger for cholesterol screening might be the visit to the GP rather than the patient's reason for that visit. Still, considering the fact that reasons for consultation relating to different health problems were registered separately, as well as the large size of the data set, and the unmistakable indications for screening such as medical examination, conclusions can be drawn from the data.

Unfortunately, the norm for hypercholesterolaemia was not standardised between the different laboratories. Analysis of file 2 does not leave us with hard data but gives a description of management by GPs of the concept of hypercholesterolaemia.

Indications for serum cholesterol measurement in 'new' patients consisted mainly of non-specific symptoms, not valid according to the guidelines. Less than 15% of all the indications were possibly indicated according to the guidelines, i.e. 6.6% concerning blood pressure measurement (possibly hypertension) and 8.1% concerning symptoms of thorax/rib (possibly angina pectoris or more likely fear of cardiovascular disease?). Serum cholesterol was measured more than once in only five percent of the patients during the three months' period. It seems unlikely that serum cholesterol was measured more than once in the other cases before or after the registration period. The number of non-specific diagnoses is remarkable, especially in 'new' patients.

We do not know what the contents and quality of the advice or information given to the patient were, nor how they were given. Recently a low rate of lifestyle advice in general practice[20] as well as a lack in communication skills regarding hypercholesterolaemia[21] have been reported. The designers of the guidelines attach great importance to extensive patient information at the moment hypercholesterolaemia is diagnosed for the first time. At the time of the National Survey, patient information was given in only half of those cases. Diet advice was given to only 14% of patients. It is possible that some diet advice was not registered but was given in another consultation outside the registration period. Despite this potential bias it is still a low number considering the fact that diet therapy is, according to the guidelines, the foundation of cholesterol-lowering therapy, deserving attention in every cholesterol-related consultation. Only three percent of the patients were referred to a dietician during the registration period. It is not known in how many cases diet advice had already been given by a dietician, so there might be underestimation.

Over 10% of pre-menopausal women with hypercholesterolaemia were treated with lipid-lowering drugs. Considering the guideline that Familial Hypercholesterolaemia is the only indication for drug treatment of pre-menopausal women, this is a fairly high percentage. In the years when the 'National Survey' was conducted, the HMG coenzyme-A reductase inhibitors were not on the market. It would be interesting to know how the prescription of cholesterol-lowering drugs has been changed, now that the HMG coenzyme-A reductase inhibitors are available. No evidence could be found for a substitution-effect between advice or diet therapy and the prescription of drugs.

Managing hypercholesterolaemia was not a clear-cut task for Dutch GPs at the time of the National Survey. The large inter-doctor variation justifies publication of guidelines for

cholesterol management in general practice. Discrepancies between daily practice and the guidelines may point at potential problems with feasibility of the guidelines. Possible barriers to change, which should be taken into account in implementing the Standard, are situated mainly in the field of indications for screening, diagnosis of hypercholesterolaemia, informing the patient when hypercholesterolaemia is diagnosed, and diet therapy as the foundation of cholesterol-lowering treatment. These are quite similar to points of attention recently assessed in the US[22]. Physicians' attitudes and motivation, rather than availability of practice guidelines, seem to relate more to actual preventive performance[23]. Further research on the implementation of cholesterol guidelines in general practice is recommended. Much improvement can be achieved in this area.

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Chapter 3

Comparison of appropriateness of cholesterol testing in general practice with the recommendations of national guidelines. An audit of patient records.

Abstract

Objective - To compare the profiles of those patients selected by general practitioners for measurement of serum cholesterol with the recommended profiles for opportunistic cholesterol testing described in the DCGP practice guidelines.

Design - Retrospective audit of 3577 adult patients' records, systematically sampled from 20 general practices.

Main measures - With criteria set by the national guidelines, the proportion of patients per practice (a) for whom cholesterol testing would be considered justified, and (b) for whom cholesterol testing would be considered unjustified, and the proportion of patients within each of these groups who had had a cholesterol measurement recorded.

Results - Cholesterol tests were performed on 11.7% of the 3577 patients. The DCGP guidelines state that a positive cardiovascular risk profile is an indication for cholesterol measurement. Just under one fifth (668) of the patients in this study were recorded as having a positive cardiovascular risk profile, but only 31% of these had had their cholesterol measured. Of the patients without recorded evidence of a positive cardiovascular risk profile cholesterol had been measured in 8%. Restricting the analyses to the age group 18-65 of whom 12.5% had a positive risk profile, did not improve the results. In practices with a computerised information system 37% of patients with recorded evidence of a positive cardiovascular risk profile had had their cholesterol measured.

Conclusions - Cholesterol testing was not targeted as selectively as recommended by the national guidelines. The major problem was failure to test those likely to benefit. Improving the targeting of cholesterol measurements would undoubtedly increase the workload of general practitioners. If the national guidelines are to have an effect on health promotion the first step must be to increase the proportion of patients with positive cardiovascular risk profiles who get their cholesterol tested. A major factor in successfully selecting cases seems to be that practices are equipped with a computerised medical information system.

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Introduction

Consensus meetings on cholesterol management in various countries, the introduction of new medication to lower cholesterol, and the portable blood testing device for cholesterol measurement, have prompted the Dutch College of General Practitioners to set guidelines for the management of hypercholesterolaemia in general practice. These guidelines, which were published in November 1991, are based on opportunistic cholesterol testing of patients with individual positive risk profiles for coronary heart disease; the use of dietary interventions is the first line intervention recommended for those with high cholesterol concentrations. Drug treatment is recommended only for those who do not respond adequately (see appendix 1).

These guidelines developed for general practitioners are similar to those published in 1987 for Dutch physicians[1] except that they recommend restricting opportunistic targeting of cholesterol measurement to those aged 18-65. Despite the publication of guidelines controversy surrounds the investigation and management of hypercholesterolaemia[2 3 4]. In our view the most important aspect of the management of hypercholesterolaemia is the first step - the targeted approach to investigation - selecting cases. More information on targeting is needed to assess both the feasibility of the guidelines in daily practice and the need for an implementation strategy. This study compares the targeting of cholesterol screening by Dutch general practitioners in routine practice with the recommendations on selecting cases set out in the guidelines.

Methods

General design

The study was based on 32 general practitioners who worked in 20 general practices. Practices were eligible for inclusion in the study if (a) there was at least one full time general practitioner; (b) they employed a practice assistant; (c) patients' records were stored in a way that allowed efficient and reproducible sampling and collection; and (d) all general practitioners in the practice were willing to participate.

In each practice patients with and without a risk profile for coronary heart disease recorded in their practice records were identified through a retrospective audit. The following data were collected in a standardised form from the records of selected patients: demographic data including age and sex; cardiovascular risk factors indicating the need for cholesterol testing; evidence of measurement of cholesterol, high density lipoprotein, low density lipoprotein, or triglycerides in the two year period 1 October 1990 to 30 September 1992. If at least one of the six risk factors mentioned in the guidelines, was recorded somewhere in the notes the patient was considered to have a positive risk profile.

Sampling and extraction of data

Guided by previous research[5 6], a sample of 10% of patients aged over 18 in each

practice was estimated to be sufficient for the purpose of this study. However, the sample size was increased to 16.5% to allow for those who did not respond to the request for use of data. To show a difference of at least 20% in the incidence of cholesterol testing between patients with and without identified cardiovascular risk factors - assuming that 5% of the patients not at risk are tested and a ratio of patients with risk to those without risk is 1:3, and applying an α of 5% and a power (1-ß) of 80% - a minimum sample size of 136 per practice is needed. We aimed to select 6000 patients' records from the 20 practices and, for reasons of feasibility, we set a maximum of 400 records per practice.

In the computerised practices, every nth patient (n depended on size of the practice population) was systematically sampled[7] from the alphabetical list of patients' records, with a standard query procedure of the computerised patient recording system. This query procedure dealt with the selection of the target group, systematic sampling, and the production of lists and labels that identified the patients included in the study. In the non-computerised practices sampling was manual. To cover an entire practice population, the planned number of patients' charts to be sampled was spread over the different filing system units. The first chart was taken randomly at the front of each filing system unit. Every fourth eligible patient was included in the sample until the calculated number of records per filing system unit had been selected.

All selected patients were sent a letter from their general practitioner asking for consent to use data from their notes. In three practices reminders had to be sent to non-responders to get the minimum number of 136 patients per practice. The data were extracted by two medical students trained in auditing records.

Statistical analysis

The average proportion of recorded cardiovascular risk factors used as criteria for targeting cholesterol testing in each practice as well as the variation in recording risk factors between practices was calculated with medians and interquartile ranges because of skewed distribution. Differences in the recording of risk profiles were analysed separately for practices with and without computerised systems for recording medical information by unpaired two tailed *t* test and Levene's test (significance level p=.05).

As well as the number of cholesterol tests done, the degree to which cholesterol tests were targeted at those with positive risk profiles was measured by cross table analysis with the following criteria: at least one serum cholesterol value recorded in the two year audit period; and at least one of the six risk factors mentioned in the guidelines in the notes. The level of targeting cholesterol testing in each practice was expressed as percentages of justified and unjustified tests (Table 1): justified tests were defined as (A/all patients) x 100; unjustified testing as (B/all patients) x 100; patients unjustifiably not tested as (C/all patients) x100; and justifiably not tested as (D/all patients) x 100. The performance scores were also analysed relatively as justified testing considering the patients with a positive risk profile (A/(A + C)x100), and justified non-testing considering the patients without a positive risk profile (D/(B + D)x100).

We separately analysed the age range 18-65 for which the case finding criteria were valid. The level of targeting of cholesterol tests in the at risk groups was also calculated separately for the subgroups of practices with and without computerised medical information systems. The difference in performance between these subgroups was tested for significance by unpaired two tailed t test (significance level P=0.05) taking the proportions per practice as a unit of analysis.

TABLE 1. CLASSIFICATION OF DIFFERENT POSSIBILITIES OF TARGETING OF CHOLESTEROL TESTING. THE RESULTS ARE PRESENTED AS THE MEAN PERCENTAGE PER PRACTICE (STANDARD DEVIATION).

	risk profile positive	risk profile not positive	
cholesterol tested	**A** 5.1 (2.3)	**B** 6.6 (3.2)	**A + B** 11.7 (4.4)
cholesterol not tested	**C** 13.2 (5.0)	**D** 75.1 (5.7)	
	A + C 18.3 (5.4)		3577 patients

Results

Characteristics of the participating general practitioners and patients

The mean (SD) age of the 32 participating general practitioners, of whom five were women, was 41 (7) years. Their working experience was 11 (8) years. Ten were working alone, the rest in association with at least one other general practitioner. The size of the practice population was 3348 (1774) patients, and the number of patients per general practitioner was 2081 (618). Twelve of the 20 practices were computerised in some form, but in only seven practices (11 general practitioners) was medical information on specific patients computerised.

A total of 6310 patients was selected through the sampling process (mean (SD) 315 (84) a practice). But informed consent was obtained from only 3950 (mean (SD, range) 65% (8%, 49%-81%); mean (SD) 197 (39) per practice). The results are based on 3577 (90% (4%)) patients (179 (39) per practice) that contacted their general practitioner during the two year audit period. The patients sampled from each of the 20 practices had similar demographic characteristics. Just under half (46%) were men. Their mean (SD) age was 45 (16) years and most 87% (6%) were between 18 and 65.

Recording cardiovascular risk factors

Individual risk factors most often recorded in patients' notes were hypertension and coronary heart disease; these were noted respectively in 10.1% and 5.3% of patient records (Table 2). General practitioners with a computerised medical information system recorded

hypertension significantly less often than general practitioners who used handwritten records. But, on the other hand, significantly more variation between practices in the number of people with recorded cardiovascular risk profiles was noted in practices that used handwritten records than for those in practices with computerised patient records.

TABLE 2. DISTRIBUTION OF THE RECORDING OF POSITIVE RISK FACTORS FOR CORONARY HEART DISEASE IN 3577 PATIENTS, EXPRESSED IN MEDIAN PERCENTAGE PER PRACTICE. QUARTILES GIVEN TO ILLUSTRATE INTER-PRACTICE VARIATION.

	median	interquartile range
CHD in patient's history	5.3	4-9
signs of familial hypercholesterolaemia	0.0	0-0
familial hyperlipidaemia in a relative	0.0	0-1
CHD in sibling or parent < 60 years	0.9	0-3
hypertension	10.1	8-16
diabetes mellitus	3.0	2-4

The mean (SD) percentage of patients in each practice with a positive risk profile (at least one of the six cardiovascular risk factors mentioned in the national guidelines) was 18.3% (5.4%). The same figure for those aged 18-65, the age group discussed in the national guidelines, was 12.5% (3.7%).

Cholesterol measurements

The mean (SD) percentage of patients per practice who had had cholesterol measured during the two year audit period was 11.7% (4.4%). This included 9.6% (3.8%) of patients aged 18-65. Although the positive risk profiles were evenly distributed between men and women in all age categories, in the 18-65 age group men were tested more often than women (men 59%, women 41%), and women aged 65 and over were twice as likely to have had their cholesterol measured than men of the same age (men 33%, women 67%).

Targeting of cholesterol testing

For a mean (SD) of 13.2% (5.0%) of patients in each practice there was no record of a cholesterol test although, according to the national guidelines, it should have been measured because of a positive risk profile (Table 3). Cholesterol tests had been done, although unnecessarily according to the national guidelines, in patients without a positive risk profile, in 6.6% (3.2%) of patients per practice. We found 668 (18.3%) patients with evidence of a positive cardiovascular risk profile recorded in their notes, of whom 31% (11%) per practice had appropriately had their cholesterol measured (A/(A+C).100). Of the patients without a positive cardiovascular risk profile, 92% (4%) per practice had appropriately not had cholesterol measured (D/(B+D.100). Similar results were obtained when the analysis was restricted to patients in the 18-65 age group.

We looked for differences in the appropriateness of the cholesterol measurement between practices with and without computerised medical information systems. The mean proportion of patients with a positive risk profile who had a cholesterol measurement recorded in their notes was 37% in practices with computerised medical information systems and 28% in practices without such equipment (p=.05). The differences in unjustified and justified lack of testing between practices with and without computerised records were also significant (p=.002 for both comparisons).

TABLE 3. PERCENTAGE OF DIFFERENT POSSIBILITIES IN THE TARGETING OF CHOLESTEROL TESTING.

practice sample size	cholesterol tested risk profile +	risk profile -	cholesterol not tested risk profile +	risk profile -
218*	4.1	5.1	9.6	81.2
231	8.7	7.8	15.2	68.4
209	1.0	1.0	23.0	75.1
223	3.1	4.5	17.0	75.3
215*	5.6	10.2	7.9	76.3
186	2.7	7.5	11.3	78.3
117*	6.0	2.6	7.7	83.8
116*	6.0	7.8	5.2	81.0
135	3.7	10.4	11.1	74.8
134	4.5	4.5	9.0	82.1
205	7.3	5.4	16.6	70.7
209	10.0	5.7	22.0	62.2
212*	5.7	7.1	9.4	77.8
216*	4.2	8.8	9.7	77.3
167	6.6	4.8	16.8	71.9
185	1.6	4.9	19.5	74.1
179	5.0	10.6	11.2	73.2
152*	4.0	1.6	12.5	82.2
134	4.5	8.2	18.7	68.7
134	7.5	13.4	11.2	67.9
mean	5.1	6.6	13.2	75.1
SD	2.3	3.2	5.0	5.7

* practices with a computerised medical information system

Discussion

We found 415 patients who had had their cholesterol measured in the two year period. But of those with a positive risk profile according the national guidelines (668 patients) only one third (31%) had had their cholesterol measured, indicating that many people are not being targeted and may therefore not receive treatment to lower cholesterol. Use of a computerised medical information system seems to improve targeting of cholesterol tests. The random samples give good insight in both doing too much and too little. We found that targeting of cholesterol tests in absolute numbers (and in percentage of the total) consists mainly of justified non-testing, so even a general practitioner who never tests any

patients may show good performance. Therefore, relative performance scores, as in the subgroup of patients with a positive risk profile, give better insights into accuracy of selecting cases.

Recent comparable audits of patients' records from the United States reported that between 55% and 67% of adults had had a cholesterol value recorded[5 8 9], but in this study of Dutch general practice we found that cholesterol was measured in only 12% of the patients. This reflects the less restrictive character of United States guidelines compared with Dutch ones; the United States guidelines recommend that all adults aged 20-70 be screened.

Underrecording is a serious limitation for general practice audits that are based on patients' notes, particularly for details of history and advice given to patients[10]. Underrecording of family history of coronary heart disease has been reported elsewhere[8]. Underrecording in this audit seemed particularly relevant for three risk factors (signs of familial hypercholesterolaemia, the presence of coronary heart disease in a sibling or parent under 60 years, and familial hyperlipidaemia in relatives). But as these three risk factors are unlikely to contribute to the histories of many patients (familial hypercholesterolaemia has been estimated to affect about one in 500[11]) our overall findings on the appropriateness of cholesterol measurement would probably not have changed much if these risk factors had been recorded properly.

The 32 general practitioners that took part in this study are in many respects (sex and list size) representative of Dutch general practitioners, but they are slightly younger and more likely to be working in group practices. Both these characteristics are reported to be factors associated with the likelihood of adopting practice guidelines[12]. Thus this audit may overestimate adherence to guidelines. It does, nevertheless, give good insight into barriers that limit adherence to national guidelines, as barriers that inhibit motivated general practitioners are to be expected in others. The difference in aptness of targeting cholesterol testing between practices with and without computerised notes could not be explained by the amount of recording of risk factors. It could be explained by the ease of accessibility of data. Obviously there may be subtle differences in the approach to practice between general practitioners working with and without this kind of computerised medical information system.

More insight is needed into other basic requirements for following preventive guidelines, one of which might be a higher level of evidence of effectiveness of the guidelines. The various cholesterol guidelines have been contradictory and controversial throughout the years. The ongoing debate about which high risk groups benefit most from cholesterol screening seems to need clarification.

We conclude that despite publication of guidelines for management of hypercholesterolaemia for all Dutch physicians in 1987 and for Dutch general practitioners in 1991 there remains considerable variation between practices in the aptness of cholesterol measurement. There is a clear need to improve the selection of those people for whom a cholesterol test is likely to be of benefit. The group that lose the most from the present situation,

which is at best only semitargeted, are those with positive risk profiles who have not had a cholesterol measurement. These people outnumber those who are tested but for whom, according to the guidelines, cholesterol measurement is inappropriate. Thus our efforts should be directed at increasing cholesterol testing in those with positive profiles. Doing this will increase the workload of general practitioners; in fact at least one in every eight adults has a positive risk profile and is in the 18-65 age group, and so should be tested. The burden on the general practitioner goes beyond a simple test, as for all those in whom cholesterol is raised repeated tests will be needed; some will require dietary advice, and some monitored drug treatment.

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Chapter 4

Trends in cholesterol testing in general practice.

Abstract

Objectives - To assess trends in cholesterol test ordering by general practitioners (GPs), and to assess whether the trend in cholesterol test ordering is consistent with the recommendations in the Dutch guidelines for GPs.

Methods - Analysis of total cholesterol and lipid fraction tests at the Maastricht diagnostic centre, which serves all 85 GPs in the region, over the years 1984-1992. Main outcome measures are the number of cholesterol, HDL, LDL, triglyceride tests per year, and the number of cholesterol tests per GP per year. The frequency of cholesterol and lipid fraction testing in 'new patients' (patients presenting for cholesterol testing for the first time) are indicators for adherence to the guidelines on the diagnostic procedure. Data on new patients were available for the years 1989-1992.

Results - There was an overall increase in the total number of cholesterol tests of 173% between 1984 and 1992. There is considerable and stable inter-doctor variation. In new patients, 13.5% of male and 23.0% of female patients did not fulfil the age criteria according to the national guidelines. Repeat testing regarding diagnosis of hypercholesterolaemia as recommended was not performed in 86% of the new patients in 1989, which increased to 94% in 1992. Lipid fraction testing during the first contact with a new patient was not recommended; nevertheless this was done in 38% of the cases in 1989, decreasing to 31% in 1992.

Conclusions and recommendations - The strong increase in cholesterol test ordering over the years was accompanied by a large and sustained inter-doctor variation in cholesterol testing. The diagnostic procedure improved slightly for lipid fraction testing, but deteriorated for repeat testing. Improvement on these topics should be sought, to prevent non-rational cholesterol management, which can have a relevant impact on GPs' workload and the resources of the public health system. In pursuing improvement, more attention should be given to effective implementation strategies as well as to the scientific validity of the guidelines.

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Introduction

Important developments on the cholesterol issue took place in the 1980s. These developments and the ongoing debate about the controversial character of cholesterol testing, raised questions whether a specific trend in cholesterol test ordering behaviour of GPs over the last decade did occur.

Considerable discrepancy between usual care and the guidelines for cholesterol management published by the Dutch College of GPs was reported before publication of these guidelines (chapter 2). Simply disseminating cholesterol guidelines does not change daily practice[1] [2]. To promote implementation of new guidelines, more insight into actual behaviour of GPs is required. In many countries a low adherence to cholesterol guidelines by GPs has been reported[3-7]. A study of possible trends in cholesterol test ordering will further explore the relation between usual care and the guidelines. It might improve insight into possible external factors that do have the potency to influence GPs in their cholesterol screening and diagnosis, or factors that restrain GPs from working according to the guidelines.

The need for information on trends in cholesterol test ordering regarding implementation of the guidelines, together with the controversial character of cholesterol testing over the years, stimulated us to address the following questions:

1. What is the trend in cholesterol and lipid fraction testing in general practice over the period 1984-1992, and which patients are being tested?
2. What is the trend in diagnostic performance in relation to the guidelines for selective case finding, repeat testing, and lipid fraction testing?

Methods

Materials

Data were used from the Diagnostic Coordinating Centre Maastricht (DCC). Since 1979, this centre processes all diagnostic requests of the GPs (about 85) in Maastricht and surroundings, covering a region with 187,000 inhabitants. All requests have been stored in a computerised database which provides a good opportunity to describe time trends. Each day these GPs 'refer' 125-150 patients to the diagnostic centre; that is, 30-35,000 patients yearly. A standardised form is used for diagnostic requests. Only regularly requested tests are printed on the form. Cholesterol and triglycerides are printed, while high density lipoproteins (HDL) and low density lipoproteins (LDL), if requested, have to be written on the form. The GPs are invited to register clinical data on the patient and the reason for the request.

Trends in cholesterol testing

To analyse the volume of test ordering in the course of time, the total number of tests per year for cholesterol, triglycerides, HDL, and LDL, were extracted from the database. The

age and sex characteristics, the reasons for request, as well as the prevalence of hypercholesterolaemia were analysed in all patients. An increase in compliance with the recommendations specified by the Dutch guidelines should subsequently result in a decreased inter-doctor variation in test ordering. For a trend analysis of inter-doctor variation in cholesterol test ordering, the GPs who had not been working during the entire year were excluded, still leaving an average of 81 GPs per year for this analysis. Due to skewed distribution, inter-doctor variation was not expressed using means and standard deviations, but using the median (= quartile 2) and quartiles 1 and 3 as indicators for inter-doctor variation. A higher inter-doctor variation, expressed as the distance between quartile 1 (Q1) and quartile 3 (Q3), may just be the consequence of an increasing median. Therefore we corrected the inter-doctor variation for the higher median by calculating the ratio (Q3 - Q1)/median.

Trends in diagnostic performance related to the guidelines

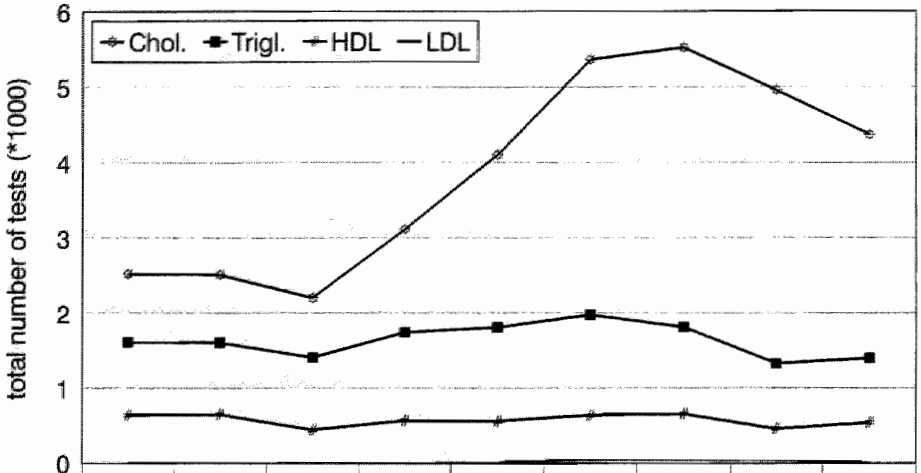
According to the national guidelines, cholesterol testing in 'new patients' (patients presenting for the first time for cholesterol testing) should be restricted to people between 18 and 65 years. Technical advances in data management made it possible to identify the subgroup of new patients for the years 1989-1992. The age and sex distribution of this subgroup, repetition of cholesterol testing, as well as the frequency of triglyceride and HDL testing were analysed. Repeat testing is indicated for patients with a cholesterol value higher than 4.9 mmol/l. Proper repeat testing in 6 weeks' time was described, in addition to a milder variant: at least one repetition of cholesterol testing in 6 months' time. Because lipid fraction testing is indicated only if cholesterol-lowering drugs are being considered, there should not be an indication for HDL or triglyceride testing in new patients. Because, instead of taking a sample, full population data of the diagnostic centre could be used, statistical testing was not indicated.

Results

Trends in cholesterol testing

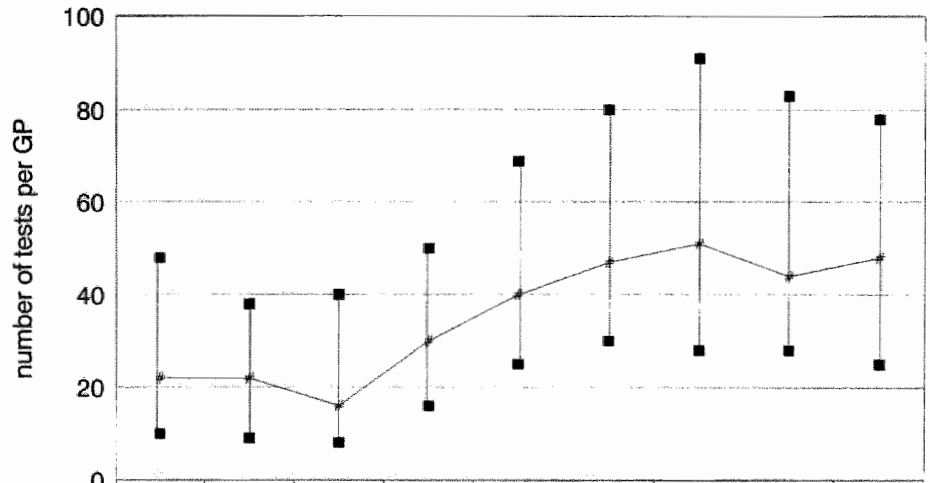
Figure 1 illustrates the trend in total number of total cholesterol, HDL, LDL, and triglyceride tests in the Maastricht region. There was an increase of 219% in cholesterol testing in the period 1984-1990, which stabilized and slightly decreased by 21% in the period 1990-1992, resulting in an overall increase of 173% between 1984-1992. There were no clear trends in triglyceride and HDL-cholesterol testing. Triglyceride testing was performed about three times more often than HDL testing in this period. LDL testing was hardly observed.

The age and sex distribution of the patients tested did not change during the 9-year period. Fifty-three percent of the patients tested were male (mean age 49 years, SD 12.9); the mean age of female patients was 55 years (SD 13.6). The prevalence of hypercholesterolaemia was already high in 1984 (51%), increased to 63% in 1987, and then decreased



	1984	1985	1986	1987	1988	1989	1990	1991	1992
Chol.	2,526	2,512	2,202	3,118	4,104	5,363	5,521	4,962	4,371
Trigl.	1,618	1,606	1,408	1,746	1,811	1,979	1,814	1,328	1,399
HDL	641	652	446	572	562	641	658	461	541
LDL	0	0	2	2	8	53	49	51	0

FIGURE 1. TREND IN TOTAL NUMBER OF CHOLESTEROL AND LIPID FRACTION TESTS AT THE DIAGNOSTIC COORDINATING CENTRE MAASTRICHT, 1984-1992.



	1984	1985	1986	1987	1988	1989	1990	1991	1992
Q3 ■	48	38	40	50	69	80	91	83	78
Median ⊕	22	22	16	30	40	47	51	44	48
Q1 ■	10	9	8	16	25	30	28	28	25
Q3-Q1/med	1,73	1,32	2	1,13	1,1	1,06	1,24	1,25	1,1

FIGURE 2. TREND IN INTER-DOCTOR VARIATION OF CHOLESTEROL TESTING PER GP, 1984-1992. MEDIAN (= QUARTILE 2) OF NUMBER OF TESTS PER GP; QUARTILE 1 (Q1) AND QUARTILE 3 (Q3) INDICATING INTER-DOCTOR VARIATION.

to 45% in 1992. The inter-doctor variation for number of serum cholesterol tests per year is illustrated in figure 2. There is considerable inter-doctor variation which, in absolute numbers, seems to have increased during the 9-year period. But, although the ratio (Q3-Q1)/median remains higher than 1.0 throughout the period, there was no clear increasing or decreasing trend in this ratio.

Trends in diagnostic performance related to the guidelines

The age and sex distribution of the new patients (patients presenting for cholesterol testing for the first time) did not change during this 4-year period (Table 1). On the average 55% of the new patients were male, of whom 13.5% did not meet the 18-65 age range which is the first criterion for selective case finding. Of the new female patients 23.0% did not meet the 18-65 age range.

TABLE 1. AGE AND SEX OF NEW PATIENTS, 1989-1992. PERCENTAGES PER TOTAL NUMBER OF NEW PATIENTS PER YEAR.

	1989		1990		1991		1992		mean	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
sex	54	46	54	46	55	45	55	45	55	45
<18 or ≥65 yrs	13	24	13	22	13	24	15	23	13.5	23.0
total new patients:	2616		3131		2439		2131			

Table 2 illustrates the number of tests used to diagnose hypercholesterolaemia per new patient per year. Proper diagnosis of hypercholesterolaemia was performed in 0.3-0.4% of the new patients. In 1989 13.7% of these patients had at least two cholesterol tests in a period of 6 months, which decreased to 6.4% of the patients in 1992. Table 3 illustrates that in 1989 GPs requested HDL and/or triglyceride tests in 37% of new patients, which is not indicated according to the guidelines. This lipid fraction testing in new patients decreased to 31% in 1992.

TABLE 2. TREND IN NUMBER OF TESTS FOR DIAGNOSIS OF HYPERCHOLESTEROLAEMIA IN NEW PATIENTS, 1989 - 1992. COLUMN PERCENTAGES OF THE GROUP OF NEW PATIENTS WITH CHOLESTEROL HIGHER THAN 4.9 MMOL/L PER YEAR.

	1989	1990	1991	1992
one test only	86.3	86.3	89.0	93.6
> 1 test in 6 months	13.3	13.4	10.7	6.1
repeat testing according to the guidelines*	0.4	0.3	0.3	0.3
new patients with cholesterol > 4.9 mmol/l	2249	2591	1941	1667

* Diagnosis of hypercholesterolaemia requires the mean of three serum cholesterol tests, determined in a period of six weeks, to be higher than 6.5 mmol/l. If the first test-value is lower than 5.0 mmol/l, or the mean of two values is lower than 6.5 mmol/l, there is no indication for (further) repetition of testing.

TABLE 3. TREND IN THE PROPORTION OF HDL AND/OR TRIGLYCERIDE TESTING IN NEW PATIENTS, HAVING A FIRST CHOLESTEROL MEASUREMENT, 1989-1992. PERCENTAGES.

	1989	1990	1991	1992
HDL, not triglycerides	3	4	3	2
HDL and triglycerides	7	7	5	8
triglycerides, not HDL	27	24	19	21
HDL and/or triglycerides	37	35	27	31
total number of 'new' patients	2616	3131	2439	2131

Discussion

Cholesterol testing by GPs affiliated to the Maastricht diagnostic centre increased by 173% in the period 1984-1992. Inter-doctor variation remained high, even after stabilisation of the increase in testing in 1990, and despite publication of Dutch cholesterol guidelines. There is considerable discrepancy between cholesterol test ordering behaviour and the guidelines. It is remarkable that, while the evidence for the benefit of cholesterol lowering is poorer for women than for men[8], relatively more women (23%) than men (13.5%) of 65 and older are tested. The poor and even deteriorating performance on repeat testing, which has also been reported elsewhere[9], is alarming because insufficient repeat testing will impair the precision of diagnoses and the cost-effectiveness of cholesterol testing[10]. Many forces seem to influence GPs' test ordering behaviour - despite the guidelines. Patients actively requesting for cholesterol testing might be one of the important determinants of GPs' behaviour in this field, as one in every five cholesterol tests was initiated by the patient in 1992 (the only year in which valid data could be collected on this aspect).
It is clear that cholesterol testing is taking far more attention and time of the GPs than 10 years ago. The high prevalence of hypercholesterolaemia gives an indication of the impact of cholesterol testing on GPs' workload, because established hypercholesterolaemia consequently implies intervening activities.

Due to large amounts of missing clinical data on the test ordering form, no analyses could be done with the patients' coronary risk profile or reasons for request. The strength of the study is the quality of the data source; considering the high number of participating practices and the fact that no apparent shifts have occurred, the population was very stable throughout the years[11]. The participating GPs were comparable to other Dutch GPs, except for the fact that GPs served by the Diagnostic Centre Maastricht have been provided twice yearly with individual feedback on selected test ordering behaviour (there has been no structural feedback on cholesterol diagnosis until now)[12]. The volume of ordering these selected tests, as well as of tests not given feedback on, decreased compared to a reference diagnostic centre. The reference diagnostic centre showed a much steeper increase in cholesterol testing of 377% over the years 1984-1990, with a comparable stabilisation in 1990. Therefore the trend found at the Maastricht diagnostic centre seems

to be an underestimation of the trends found in other Dutch diagnostic centres.

What are the implications of the results for implementation of the guidelines? The discrepancy between cholesterol test ordering behaviour and the guidelines does not necessarily mean low quality of care. Guidelines imply little performance measurement, as medical practice remains fundamentally an interpersonal experience, drawing on the rich interaction between practitioner and patient[13]. Physicians cite barriers for adherence to the guidelines such as: limitations in time, reimbursement, motivation, and skills[14-16]. Based on the barriers to change, a complex programme for improvement, that meets prevailing administrative and reimbursement policies[17], is needed with a mix of several strategies for implementation[18-21]; eg. individualised feedback on the GPs' test ordering behaviour, in combination with strategies such as an adjustment of the test ordering form, small group peer discussions, or outreach visits of academic detailers or local opinion leaders. To increase the likelihood of the guidelines changing medical practice, the feasibility of the guidelines should be discussed at local level[22].

In addition to a discussion on the implementation of the guidelines, the results prompt a critical look upon scientific validity of the guidelines. The ongoing debate about which high-risk group benefits most by cholesterol screening needs clarification. It is remarkable that the practice guidelines that have been published internationally are conflicting in several aspects. Cholesterol guidelines seem to be influenced more by moral and economic factors than by evidence of health benefit[23 24]. The method of developing the guidelines determines the scientific validity of the guidelines[25 26]. Recently, a method for grading health care recommendations was proposed in which both scientific validity and cost-effectiveness considerations (number needed to treat) are combined[27 28].

We conclude that the strong increase in cholesterol test ordering over the years was not accompanied by a decrease in inter-doctor variation and improvement in quality of testing. We recommend that improvement on these topics should be sought, to prevent non-rational cholesterol management. In pursuing improvement, more attention should be given to effective implementation strategies as well as to the scientific validity of the guidelines.

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Feasibility of cholesterol guidelines

The feasibility of the guidelines is investigated in chapters 5 and 6 by applicating a programme for improvement in 10 general practices. Possible barriers to adherence to the guidelines were investigated and a programme for improvement, based on these barriers to change, is described in appendix 2. The effect of the programme for improvement on actual performance is described in chapter 5. The influence of the programme for improvement on the GPs' knowledge of and attitude towards the cholesterol guidelines is described in chapter 6, as well as the barriers to change experienced by the group of GPs participating in the trial.

Chapter 5

Effect of implementation of cholesterol guidelines on performance.
A randomised controlled trial in 20 general practices.

Abstract

Objectives - To evaluate the feasibility of cholesterol guidelines by assessing the effectiveness of implementation of these guidelines on actual performance of Dutch general practitioners (GPs).

Design - Randomised controlled trial.

Setting and subjects - 32 GPs in 20 general practices, 3950 patient records, 594 registered patient contacts.

Interventions - A 5-month programme for improvement, developed after barriers to working according to the guidelines had been investigated, consisted of group education, desktop supportive materials, feedback on performance, and face-to-face instruction on location.

Main outcome measures - The outcome parameters were defined as quality of selective case finding, quality of diagnostic procedures, and therapeutic quality, and measured by chart audit and self-administered consultation registration.

Results - The quality of selective case finding, especially the targeting of cholesterol testing to those with positive cardiovascular risk profiles, did not improve following intervention. Performance of the procedure necessary to diagnose hypercholesterolaemia even deteriorated, and the application of diet therapy also decreased following intervention. The quantity of cholesterol testing increased in both groups, but this was largely explained by the increased availability of desktop cholesterol analysers. In 41% of the contacts in which patients were tested they had actively requested for it.

Conclusions - An intensive programme for improvement had no measurable impact on actual performance on working according to the cholesterol guidelines. Both the validity and the opinion about feasibility of the guidelines in daily practice deserve more attention during guideline development.

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Introduction

The results of the studies described in chapter 2 till 4 led to the conclusion that a well-designed strategy is needed to implement the cholesterol guidelines of the Dutch College of GPs. Knowledge of guidelines does not necessarily lead to compliance with those guidelines[1-3]. Moreover, knowledge about effective methods of bringing about specific changes in clinical behaviour is sparse[4]. The effectiveness of traditional education to change physicians' behaviour is to be doubted[5]. It may affect knowledge and beliefs, but rarely results in behaviour change[6].

Previous studies evaluating implementation of guidelines on cholesterol differed in their effectiveness in changing physicians' behaviour. Several interventional strategies, in several combinations, were used, such as group education, educational or supportive materials, feedback on performance, general/patient-specific reminders, and incentives[7-10]. None of these studies were (completely) conducted in the primary care setting. Recently, a randomised trial was reported on the effect of intensive continuing medical education on the compliance to cholesterol guidelines by American primary care physicians[11]. The intervention, mainly in lecture format, did not show any effect. In none of these studies was an analysis of physicians' needs performed in developing the intervention, which is an important factor for the potential for change of implementation strategies[12]. This paper presents the results of a randomised trial evaluating the effects of an implementation programme, designed to enhance the adherence of general practitioners to working according to the Dutch guidelines on cholesterol. We aimed at optimising the implementation strategy by assessment of the barriers and needs perceived by GPs to working according to the guidelines (appendix 2).

The objective was to assess the effects of a programme for improvement on GPs' actual performance in daily practice, taking the DCGP national cholesterol guidelines as a reference, in order to test the feasibility of the guidelines.

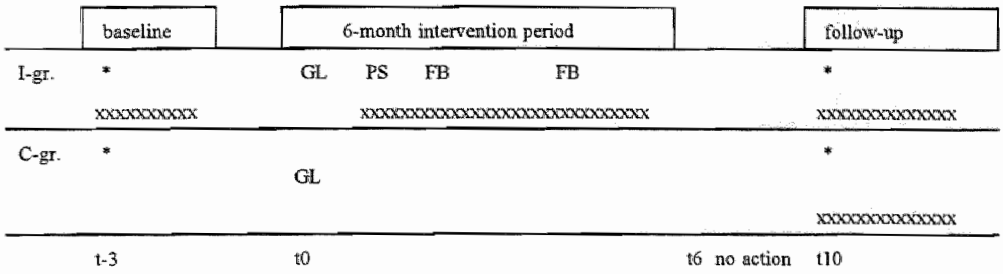
Methods

Study design

A randomised controlled trial with a 6-month intervention period was conducted in 20 practices. The guidelines, together with a set of scientific background materials, were distributed to all participating GPs. Implementation took place in half of the general practices, the other half serving as controls. The inclusion criteria for participating practices were employment of at least one full-time GP, employment of a practice assistant, the availability of an acceptable patient registration system, and, in the case of group practices, participation of all GPs of that practice. Comparability of the two groups was assured by means of stratified randomisation, with the following strata: computerised medical information system (yes/no), type of practice (solo/group), and size of practice ($<2500/\geq 2500$ patients). After stratification, practices were randomised with a permutated

block design to ensure exactly equal group numbers. If strata were filled with less than two practices, practices that were most alike were put together in a block. The follow-up measurement started three months after the intervention was completed, in order to measure maintenance of changed behaviour (Figure 1).

FIGURE 1. STUDY DESIGN; TIME SCHEDULE FOR INTERVENTION GROUP (I-GROUP) AND CONTROL GROUP (C-GROUP) SEPARATELY



* Chart audit; baseline 24 months retrospection, follow-up 9 months retrospection
xxxxx Self-administered consultation registration, with general reminders during the intervention period
GL distribution of guidelines
PS plenary session
FB feedback and face-to-face instruction at location

The programme for improvement

The programme for improvement is extensively described in appendix 2. In short; It started with a 3-hour educational session chaired by a local opinion leader, a month after the guidelines had been distributed. During this session the GPs were provided with several supportive materials such as consultation registration forms, a desktop flow chart of the guidelines, and a sufficient supply of patient education leaflets. Guideline topics where Dutch GPs had shown barriers to change or educational needs were discussed and thorough education was provided. The rest of the programme consisted of continuous recording of 'cholesterol consultations' by the GPs, using standardised registration forms. During two outreach visits by one of the authors (TvdW) feedback on performance was given based on the registered consultations, which led to face-to-face instruction or further discussion on guideline topics and barriers to change. The only intervention in the control group was the postal distribution of the guidelines with its scientific background materials.

Effect parameters and instruments

Effect parameters were defined in three different areas; The quality of selective case finding, the quality of diagnostic procedures, and therapeutic quality.

Quality of selective case finding refers to the targeting of cholesterol testing at the patients with at least one of the six risk factors mentioned in the guidelines, to be called

'positive risk profile'. It was expressed in proportions: justified testing as (risk profile+ and test+/all patients)x100; unjustified testing as (risk profile- and test+/all patients)x100; unjustified not testing as (risk profile+ and test-/all patients)x100, and justified not testing as (risk profile- and test-/all patients)x100 (see page 30, Table 1). A summarising, comprehensive measure for these proportions is the odds ratio. An odds ratio significantly greater than 1.0 (the lower limit of the 95%-exact confidence interval is greater than 1.0) means that having a positive risk profile increases the chance that the patient has a cholesterol value recorded (the ratio of the test/non-test odds among those with a positive risk profile and the test/non-test odds among those those with a negative risk profile). The higher the odds ratio, the more selective is the case finding.

Diagnostic quality refers to the recommendation that a properly diagnosed hypercholesterolaemia requires at least two measurements. This was expressed as at least one repetition of cholesterol testing in a period of 6 weeks in patients with a cholesterol level higher than 5.0 mmol/l (if cholesterol is lower than 5.0 mmol/l at the first measurement, no further testing is required).

Therapeutic quality was defined by two guideline issues. First, it was expressed as the frequency of diet therapy. The guideline emphasises the importance of diet therapy as the basis of cholesterol-lowering therapy. Second, therapeutic quality was expressed as the selectiveness in prescribing cholesterol-lowering drugs to those that do not respond to diet therapy, using the following criteria: the patient had a serum cholesterol higher than 6.5 mmol/l; hypercholesterolaemia was established at least 6 months ago; the patient had a positive risk profile.

The effects of the intervention were measured by chart audit; patient records of random samples of 10% of all patients aged 18 years or older were taken in the 20 general practices (see page 29). At baseline the whole patient record was reviewed for notes on coronary heart disease or CHD risk factors, while for notes on lipid diagnosis or therapy the audit was limited to the period of two years before the moment of randomisation. At follow-up the patient record was reviewed for the 9 months from the moment the intervention started (Figure 1). The chart audit was performed by two medical students, who were blind to study group assignments.

To compensate for under-recording, which may pose a problem in chart audit, a second instrument was used to measure performance. The GPs were asked to register all the consultations in which cholesterol was a topic (just talking about it was already a reason to register) during a period of 8 weeks at follow-up (Figure 1). The GPs in the intervention group had also registered consultations for a period of 8 weeks at baseline, in order to gain insight into their own performance. The registration form contained open questions and multiple choice items with a mix of right and wrong options.

Data analysis

Chart audit: The odds ratios per practice were pooled in an overall odds ratio across the practices per group, using the Mantel-Haenszel method for combining data from 2x2

tables. The difference in selective case finding performance between groups was tested with the Mann-Whitney-Wilcoxon rank-sum test (significance level p=.05) of the log odds ratios. In a subgroup analysis we accounted for the age range of 18-65 years (the recommended age group). We checked for the influence of a computerised medical information system in an additional subgroup analysis between practices with and without a computerised patient registration system used for recording patient-specific medical information.
To control for the difference in time range of the baseline and follow-up period (24 and 9 months respectively), the data of the 2-year period were standardised to the data on the 9-month period by analysing with patient-years as the time denominator. This was done for justified testing among all the patients with a positive risk profile and for justified non-testing among all patients with a negative risk profile. The scores were tested for pre-post differences between groups with unpaired two-tailed t-tests (significance level p=.05).

The analyses at practice level, with the chart audit results clustered to each practice, is suboptimal due to variation in number of patients across practices. The alternative of an ordinary logistic regression analysis with patients as unit of analysis may suffer of type I error due to dependence between outcome of patients within the same practice. Therefore a multi level analysis was performed, using the EGRET 1995 statistical package (version 1.02.10). A random effects logistic regression analysis was performed to control for this dependence (the intra class correlation) by including practice as random effect and patients as unit of analysis. The dependent variable was the cholesterol test done or not done during follow-up. Independent variables in the model were the intervention, the patient's risk profile at follow-up, age and sex of the patients, a binary quality score of the selective case finding performance at baseline, and the interaction between risk profile and intervention.

To describe diagnostic quality, the frequency of testing was analysed in the patients in whom no cholesterol value or lipid-lowering therapy was recorded in the foregoing year (repeat testing for monitoring is not recommended). The proportion per practice of these patients for whom repeat testing was correctly performed was calculated. Because of skewed distribution, the difference between groups was analysed with the Mann-Whitney-Wilcoxon rank sum test. In subgroup analyses the diagnostic quality was analysed for the group of patients aged 18-65 years and then for the group of patients aged 18-65 years with a positive risk profile. Analyses on diet and drug therapy were not reported because of small numbers.

Consultation registration: The registered patient contacts were analysed at the GP level, therefore the sample size is n = 32. Quality of selective case finding was determined by cross-table analysis with the same criteria as described for chart audit, but only for the patients tested on cholesterol. The registration period of 8 weeks is too short to draw conclusions on non-tested patients; therefore only the proportions of justified testing among all patients being tested per practice during the registration period were described. Pre-post difference in the intervention group and between-group difference at follow-up were tested with the Mann-Whitney-Wilcoxon rank sum test (significance level p=.05).

Frequencies of therapeutic performance were calculated, and between-group differences were tested with the unpaired two-tailed t-test (significance level p=.05).

Results

Characteristics of practices and GPs

Thirty-two GPs were working in the 20 participating practices. Ten of the participating GPs were working single-handed, the others were working in 10 practices with one or more partners. The mean age of the GPs (5 women) was 41 years (SD 7.4). The stratified randomisation procedure ascertained comparability of groups on most criteria (Table 1). There were some differences, some of which reached the level of significance: the GPs from the control group were on average 5 years younger and had less work experience. Twelve of the 20 practices were computerised, but only in 7 practices (11 GPs) was patient-specific *medical* information recorded in the computerised medical information system. At baseline 2 intervention and 3 control practices possessed desktop cholesterol analysers. This possession doubled at follow-up; half of the intervention as well as half of the control practices had equipped themselves with a desktop cholesterol analyser.

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY GROUPS IN ABSOLUTE NUMBERS OR PERCENTAGES (STANDARD DEVIATIONS)

		I-group (SD)	C-group (SD)
variables in stratification		n=10	n=10
type of practice	solo	5	5
	duo	2	2
	group/health centre	3	3
number of practices with ≥ 2500 patients		6	6
computerised	no	3	3
	yes	7	7
	(yes, medical module)	4	3
participants		n=16	n=16
age (yrs)		43.5 (8.7)	38.3 (4.9)*
work experience (yrs)		14.0 (8.6)	8.4 (5.8)*
sex	♂	15	12
	♀	1	4
CME cholesterol	none	10	9
	CME group	1	1
	self-study	2	3
	other	3	2

* $p<0.05$ (two-tailed unpaired t-test)

After sampling in the 20 practices 3950 patient records have been audited. On average 90% of the patients had actually contacted their GP at baseline (179 (SD 39) patients per practice), and 79% of the patients at follow-up (156 (SD 34) patients per practice). The patient samples in the intervention and control group were comparable for relevant

demographic characteristics. During the 8-week baseline period the 16 GPs in the intervention group registered on average 15 (SD 9) consultations per GP (in total 239 consultations of 222 patients). During the 8-week follow-up period 15 GPs from the intervention and 15 GPs from the control group registered 11.5 (SD 8) and 13 (SD 9) consultations per GP respectively. This was in total 173 consultations of 155 patients in the intervention group and 182 consultations of 167 patients in the control group. One GP dropped out from the intervention group because of early retirement, and one GP who switched to another practice dropped out from the control group.

Quality of selective case finding

Chart audit: The case finding performance is presented in odds ratios per practice to show inter-practice variation (Table 2). No effect of the intervention was found; the likelihood for a patient with a positive risk profile to have his or her serum cholesterol tested and recorded did not increase. Instead of higher odds ratios, lower odds ratios were seen during the follow-up period. The number of significantly positive odds ratios decreased at follow-up, especially in the intervention group. Nevertheless, the pooled odds ratio remains higher in the intervention group because the performance of the GP in one general practice strongly improved (odds ratio 49.5). Moreover, the quality of case finding neither improved in the subgroup of patients aged 18 to 65 years. The seven practices equipped with a computerised medical information system showed significantly better performance on selective case finding than the other practices during the baseline period ($p=0.0034$), but not during the follow-up period ($p=0.39$).

TABLE 2. PERFORMANCE SCORES ON SELECTIVE CASE FINDING (CHART AUDIT). ODDS RATIOS PRESENTED PER PRACTICE AND POOLED ODDS RATIOS (95% EXACT CI) PRESENTED PER GROUP.

intervention practices	baseline	follow-up	control practices	baseline	follow-up
1#	6.9*	22.9*	1	5.8*	5.3*
2	5.0*	5.4*	2	4.9*	3.4*
3	3.3	3.3	3#	6.6*	2.9*
4	3.1*	3.0*	4#	3.8*	18.4*
5#	5.3*	3.1	5	5.9*	3.5*
6	2.5	2.9	6	1.3	1.8
7#	25.4*	5.3	7	3.1*	1.8
8#	12.2*	3.0	8#	19.7*	11.2*
9	2.4	2.5	9	2.0	21.1*
10	9.2*	49.5*	10	3.4*	4.3
pooled OR:	5.1	4.9		4.2	3.8
95% CI:	3.7-7.4	3.1-8.4		3.1-5.8	2.6-5.9

\# practices with a computerised medical information system, including the medical module
* significant odds ratios, the lower limit of the 95%-exact confidence interval is greater than 1.0)

Adjustment for patient-years in the analyses did not show any differences between intervention and control group in the amount of pre-post changing in performance.

The multi level random effects logistic regression analysis, using 2768 observations, did not show an effect of the intervention either. The interaction variable was left out because it was far from significant. The odds ratio was 0.76 (95%CI 0.44-1.30). Although there appears to be an inhibiting effect of the intervention with regard to testing, no statistically significant and clinically relevant effect of the intervention was seen.

Consultation registration: Case finding performance for patients who had their cholesterol tested is described in table 3. For the average 80% of the patients who were tested at baseline, this was justified according the guidelines because they had a positive cardiovascular risk profile. At follow-up this was 81%, which did not differ significantly from the control group (70%). In the consultations in which the patient was going to be tested, it was not uncommon for the patient to actively request for the cholesterol test. This was the case in 30% of the patient contacts at baseline, and 41% at follow-up.

Diagnostic quality

Chart audit: There were 415 patients during the baseline and 193 patients during the follow-up period with a diagnostic cholesterol value recorded on their record. At baseline 53 (SD 22) cholesterol tests per 1000 patient-years were audited per practice in the intervention group, and 63 (SD 22) in the control group. At follow-up the number of cholesterol tests per 1000 patient-years increased in both groups: 72 (SD 39) in the intervention and 96 (SD 38) in the control practices. The increase in cholesterol testing was significantly higher (p=.033) in the practices that were equipped with a desktop cholesterol analyser.

The median proportion of patients for whom the GP performed repeat testing to diagnose hypercholesterolaemia was low in both groups during the baseline period (I-group: 11.8 (P_{25} 4.4, P_{75} 28.8) and C-group: 13.4 (P_{25} 8.2, P_{75} 18.8)), and decreased to zero in both groups at follow-up (I-group: 0.0 (P_{25} 0.0, P_{75} 24.5) and C-group: 0.0 (P_{25} 0.0, P_{75} 13.3)). Comparable results were found in the subgroup of patients aged 18 to 65 years with a positive risk profile.

TABLE 3. CASE FINDING PERFORMANCE BASED ON CONSULTATION REGISTRATION. TOTAL NUMBER OF PATIENTS TESTED PER GROUP, AND THE NUMBER OF PATIENTS BEING JUSTIFIABLY TESTED (HAVING A POSITIVE RISK PROFILE) PER GROUP, AND THE MEAN PROPORTION PER PRACTICE (SE MEAN).

	baseline		follow-up	
	I-group	C-group	I-group	C-group
- number of patients tested	114	-	103	79
- number of patients justifiably tested	90	-	84	58
- mean proportion of patients justifiably tested per practice	80% (5)	-	81% (8)	70% (8)

Therapeutic quality

Consultation registration: Prescription of diet-therapy was registered in the intervention group in 38% of the consultations at baseline. During follow-up this was 30% and 41% for the control group. Cholesterol-lowering drug therapy was registered in the intervention group in 18% of the consultations at baseline. During follow-up this was 13% and 21% for the control group.

Discussion

No effect of an intensive strategy to implement national guidelines on hypercholesterolaemia could be demonstrated. There was, first of all, no difference (in pre-post change) between the groups for the quality of selective case finding. At baseline the quality of selective case finding seemed to depend particularly on the availability of a computerised medical information system. At follow-up this factor no longer differentiated the performance between practices. Although cholesterol testing did not improve qualitatively, it did increase quantitatively. The positive association that was found between cholesterol testing and the availability of desktop testing device was also reported by others[13-15]. The large number of patients actively requesting cholesterol testing (about 40% of the patients tested at follow-up) might be another factor associated with this increase in testing. This kind of external influence, like the demanding patient or marketing activities of drug companies who provide desktop test devices, might play a major role in the cholesterol screening activities of GPs, may be more decisive than the intervention. The low and even deteriorating performance on the diagnosis of hypercholesterolaemia, the stepwise repeat testing of serum cholesterol, is alarming. Apparently, this is a major problem in daily practice, also reported by American physicians[16].

Could a real difference between the intervention and control group exist without being detected (type II error)? It is highly unlikely, considering the lack of improvement - deterioration is even seen after application of the solid intervention - that the direction of the results would have changed if a larger group of general practices would have been involved. The most appropriate analysis, the multi level analysis, based on a sample size n=2768, did not show any effect of the intervention. The other outcomes of this trial, see also chapter 6 for results of the intervention on the GPs' knowledge and attitude, point at the same direction.

Although the registered consultations neither showed an intervention effect on the quality of selective case finding, it revealed rather high quality in comparison with the performance described by chart audit. This might be explained by the fact that GPs do not record all the information that they are actually aware of about the risk profile of their patients[17], while they were forced to fill in their knowledge about a patient's risk profile during the registration of a consultation. So, the results of chart audit probably underestimate the category of patients justifiably tested and overestimate the category of patients unjustifiably tested. This registration bias was clearly demonstrated in the underrecording

of diet therapy on the patient record. During the consultation registration period of 8 weeks a higher number of patients with diet therapy were recorded than during the chart audit over 24 months.

Why did the intervention not work? Although there may be methodological restrictions to this study, we believe it is very unlikely that a strong effect was hidden. We had even tried to maximise the contrast between the groups by not letting the control group GPs register cholesterol contacts during baseline (measuring behaviour may have an intervening effect, the Hawthorne effect[18]). According to the educational and behaviour change theories, this implementation programme ought to be a solid intervention. Apparently there is more to implementation of practice guidelines than the behaviour change theories deal with. It might be a prerequisite for successful implementation of guidelines with a controversial character that the GPs themselves internalise the guidelines in their own localised consensus procedure[19].

Also features of the guidelines itself may have impeded its implementation. For instance, the preventive character of the cholesterol topic. Nearly all or at least a majority of the GPs see CHD-prevention as an important task[20-24]. Despite this belief in preventive care, actual preventive performance is low. Physician-oriented approaches to implement preventive services seem to lack efficacy[25]. The barriers for adherence to cholesterol guidelines described in the literature resemble the barriers we found: limitations in or lack of time, reimbursement, motivation, practice organisation, adequate dietary counselling skills, patient compliance, and not feeling at ease in intervening with the patient's lifestyle[21-23 26-28]. The role and responsibilities of the GP in the field of prevention are disputed by others. Doctors are educated and prepared for investigating symptomatic patients and caring and curing the sick, rather than for keeping the healthy ones healthy. Preventive medicine may disturb this function[28 29].

Furthermore, the guidelines might just not be good enough[30]. The method of developing the guidelines determines the scientific validity of the guidelines[31 32]. While many GPs believe that good practice is not always necessarily based on scientific evidence[33], the scientific validity of the guidelines has not gone unquestioned. In addition, the publications on various cholesterol guidelines have been contradictory and controversial throughout the years. The ongoing debate about which high-risk groups benefit most by cholesterol screening seems to need clarification by the GP. A higher level of evidence might be needed, accompanied by descriptions of the strength of the evidence, as well as information on cost-effectiveness in the primary health care setting, to convince GPs of the importance of certain guidelines[34]. At least guidelines should be clear and user-friendly, which, according to the GPs, is not the case with the cholesterol guidelines. One of the stumbling blocks, besides the complex substance of the guidelines, may be the presentation[35]. It would be of great interest to know whether a less complicated set of guidelines would have greater applicability and more widespread public health effects.

It can be concluded that the implementation programme had hardly any relevant impact on working according to the guidelines. It may have been too early for promoting

implementation of cholesterol guidelines in general practice, due to the controversial character of the guidelines. Much attention should be given to both the scientific validity of the guidelines, including cost-effectiveness of cholesterol lowering in general practice, and the feasibility in daily practice during the process of development or updating of guidelines.

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Chapter 6

Barriers to working according to cholesterol guidelines. A randomised controlled trial on implementation of national guidelines in 20 general practices.

Abstract

Background - The objective was to test the feasibility of cholesterol guidelines for Dutch general practitioners (GPs). Knowledge and favourable attitudes are fundamental to the adoption of these guidelines and need to be optimised for successful implementation of the guidelines. The effect of a programme designed to improve these basic requirements was assessed, and the barriers to change were investigated.

Methods - The cholesterol guidelines were distributed to 32 GPs in 20 general practices. The study was conducted as an RCT with a 6-month intervention period. The programme for improvement consisted of group education, feedback on performance, and face-to-face instruction on location.

Results - The GPs increased their knowledge of the guidelines significantly after the educational session, but their score decreased to a lower level than the mean score of the control GPs at follow-up. The level of agreement with the guidelines was already rather high at baseline and remained comparable for both groups at follow-up. The GPs' opinion of feasibility of the guidelines, in contrast, was rather low at baseline and remained low at follow-up. Important barriers to change were the complexity of the guideline algorithm, the amount of time needed for this type of care, the difficulty to perform selective case finding, and guidance of diet therapy.

Conclusions - An intensive programme for improvement had hardly any impact on basic requirements for adherence to the cholesterol guidelines. Both the validity of the guidelines and the opinion about feasibility of the guidelines deserve more attention during guideline development.

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Introduction

Simply disseminating cholesterol guidelines already proved to be not effective[1]. Nearly 80% of Canadian GPs knew about and agreed with national cholesterol guidelines, but as few as five percent of them actually followed the guidelines[2]. Studies on implementing a set of preventive guidelines in general practice, applying strategies like feedback and reminders, show disappointing results on cholesterol screening[3 4 5]. Other implementation studies which focused specifically on cholesterol guidelines showed varying results. Therapeutic management of inpatients with hypercholesterolaemia did improve with feedback and reminders[6]. An intense implementation programme led to a small improvement in knowledge and attitude[7], and a small change in actual performance[8]. Actual performance did not improve in another trial although attitude towards and knowledge of the guidelines had been optimalized[9].

Apparently, implementing cholesterol guidelines is a complex process and specific implementation strategies are needed. A combination of several strategies, linked to the barriers to adhere to the guidelines is advocated[10 11 12]. Three major groups of factors are regarded as affecting behaviour: predisposing factors (e.g. knowledge, attitudes) which predispose an individual to take action, enabling factors (e.g. skills) which enable a particular behaviour to occur, and reinforcing factors (e.g. attitudes of peers) which reinforce and tend to maintain new behaviours[13]. The objective of this study was to assess the effect of a programme for improving knowledge of and attitudes towards the cholesterol guidelines and to investigate the barriers to working according to these guidelines.

Methods

Study design

A randomised controlled trial was conducted with a follow-up measurement one year after baseline and a 6-month intervention period in between. The guidelines were disseminated in all the participating practices and implemented in half of these by an intense programme for improvement, the other 10 serving as controls. The follow-up measurement took place three months after the intervention was completed. This 3-month period without action was introduced in order to measure maintenance of changes rather than immediate effects. In addition, in order to further evaluate the barriers, a cross-sectional study was carried out in the intervention group during the 6-month intervention period.

The following inclusion criteria were used for participating practices: a practice should have at least one full-time GP, employ a practice assistant, and have an acceptable patient registration system, and, in case of group practices, all GPs of that practice should participate. The GPs were offered a financial compensation for participating in the study. Various strategies were applied to recruit practices (notices in the newsletters of as well as personal contacts with the regional (in)formal networks of general practitioners), until 20

participating practices were found. Comparability of the two groups was assured by means of stratified randomisation at the practice level, with the following strata; computerized medical information system (yes/no), type of practice (single handed/group), and size of practice (<2500/≥2500 patients). Computerisation of the patient registration system seems to assist the GP in performing selective case finding[4]. In addition, GPs working in group practices might be more willing to change their practice habits as they are directly influenced by cooperating with colleagues, and the size of the practice population might be an indication of the workload of the GP.

The programme for improvement

After assessment of the usual care (chapter 2 and 3), which provided insight into possible barriers and needs to working according to the guidelines, a programme for improvement combining various interventions, was developed with specific implementation strategies (see appendix 2). This programme started with the postal distribution of the guidelines with scientific background materials. It was followed by a 3-hour plenary session chaired by a local opinion leader a month later. The session consisted of a lecture followed by discussion in small groups and a skill training workshop using imaginary patient cases. Guideline topics for which the GPs had shown lack of insight were discussed thoroughly. The GPs were provided with several supportive materials such as consultation registration forms, a desktop flow chart of the guidelines, and a sufficient supply of patient education leaflets. The rest of the programme consisted of a 5-month period of recording of consecutive 'cholesterol consultations' by the GPs. The consultation registration forms were constructed in such a way, using inserts with the key items of the guidelines, that the GPs got immediate feedback on their performance. Therefore, the registration of cholesterol consultations can be looked upon as general and patient-specific reminders[14]. During two outreach visits by one of the authors (TvdW) further education was given. Feedback on performance based on the registered consultations was also provided, which led to face-to-face instruction and further discussion on guidelines topics and barriers to change. The only intervention that the GPs in the control group experienced was the postal distribution of the guidelines with scientific background materials.

Measurements and data analysis

A knowledge test and an attitude questionnaire were developed to measure the effect of the intervention on basic requirements for behaviour changes. The barriers to change were investigated by qualitative research[15].

The knowledge test was constructed by a group of experienced test-writers[16]. Content validity was assured by selection of the key-items by a consensus procedure which included the composers of the standard on cholesterol. The 30 key-items were of the true/false/question mark type. Construct validity was investigated by submitting parallel tests to GPs and trainees in general practice (n = 104), immediately before and directly after continuing education on the DCGP cholesterol guidelines, as well as eight months

later. The group differences related to the participation in continuing education programmes supported the contruct validity of the test[16]. Reliability turned out to be too low to attach consequences to individual test scores, but the mean group scores are reliable enough to warrant the use of the test in evaluation studies[16]. The knowledge test was executed just before and after the plenary session for the GPs in the intervention group, and at the practice site for the GPs in the control group, and a follow-up post-test was taken during follow-up. The tests were taken under proper examining conditions[17]. The scores on the test were calculated as percentages of the true minus false scores. Differences within and between groups were tested with the t-test, with a 0.05 level of significance.

The attitude questionnaire consisted of nine questions concerning scientific attitudes towards the cholesterol guidelines, and 17 questions concerning opinions about the feasibility of the guidelines in daily practice. These questions were based on the 30 key-items mentioned above. The effect parameter was the proportion per group of answers corresponding with the guidelines. Differences between groups were tested with the Mann-Whitney U Wilcoxon Rank Sum test (two-tailed significance level p=.05).

A multiple linear regression analysis model was used to control the effect of the intervention for baseline differences between groups. The variables for which baseline differences were found, the variables used to define the strata, and the total mean baseline scores on attitude and on opinion on feasibility were included in the model as independent variables. Dependent variables were the total mean scores at follow up on attitude towards and on opinion about feasibility of the guidelines.

Barriers to change. During the last outreach visit, which was at the end of the intervention period, the GPs were asked in semi-structured interviews what they had experienced as the main barriers for working according to the guidelines. In order to underline the barriers with empirical data, the consultation registration forms, which were filled in by the GPs during the intervention period, were analysed by descriptive statistics. This gave insight into the frequency of occurrence of the several guideline topics on contact level.

Results

Characteristics of practices and GPs. Thirty-two GPs were working in the 20 participating practices. The mean age of the GPs, of whom five were women, was 41 years (SD 7.4). Twelve of the 20 practices were computerised, but only in seven practices (11 GPs) was patient-specific *medical* information recorded in the computerised medical information system. Ten of the participating GPs were working single-handed, the others were working in 10 practices with one or more partners. The stratified randomisation procedure ascertained comparability of groups on practice criteria but there were some differences at GP level; the GPs from the control group were on average five years younger and had less work experience (see page 50, table 1).

GP knowledge on the cholesterol guidelines. The baseline knowledge true-false scores were slightly higher for the control group than for the intervention group, namely 49% versus 43%. The post-test mean score, at the end of the educational group session, significantly increased to 74% in the intervention group. At follow-up the knowledge test score was higher for the control GPs (53%) than for the intervention GPs (51%). The net increase in knowledge was eight percent for the intervention group in comparison with four percent for the control group, but the difference was not statistically significant.

GP attitudes towards the guidelines. There were no differences in agreement at baseline (Table 1). At follow-up the degree of agreement had increased for both groups, the increase being a bit higher for the intervention group. This difference in increase was only significant for one topic; the guideline about advising the patient to cease smoking first before screening for hypercholesterolaemia. At follow-up there was 100% agreement with the guideline for selective case finding in the intervention group. Most GPs disagreed with the guideline that the patient should be referred to a specialist in case of familial hypercholesterolaemia. The agreement with the guidelines on diet and drug therapy was rather high.

TABLE 1. RESULTS OF THE QUESTIONNAIRE ON ATTITUDE TOWARDS THE GUIDELINES. PROPORTION OF GPS AGREEING WITH A GUIDELINE TOPIC. (ANSWER CATEGORIES: AGREE = 1, DISAGREE = 0)

	baseline		follow-up		
	I-group n=16	C-group n=16	I-group n=16	C-group n=16	
'perform selective case finding'	0.88	0.88	1.00	0.94	
'patient registration system is suitable'	0.75	0.88	0.81	0.81	
'advise to cease smoking first'	0.56	0.50	0.94	0.53*	##
'perform supplementary lab-examination on suspicion only'	0.31	0.38	0.44	0.63	
'refer in case of Fam. Hypercholest.'	0.38	0.50	0.44	0.44	
'start with diet therapy (before drugs)'	0.69	0.88	0.88	0.81	
'use specified patient education material'	0.94	0.87	0.94	0.75	
'continue diet for another 6 months'	0.56	0.75	0.75	0.69	
'consider drugs after unsuccessful diet'	0.75	0.88	0.88	0.94	

*/** $p<0.05$ on difference between groups/ on pre-post differences between groups (two-tailed Mann-Whitney U test)
#/## $p<0.10$ on difference between groups/ on pre-post differences between groups

The GPs in both groups showed more or less similar opinions about feasibility of the guidelines except for two items: a higher belief in feasibility of continuing diet therapy for another six months and in feasibility of the advice to cease smoking first in the intervention group compared to the control group at follow-up (Table 2). The opinion about feasibility of the guidelines was, in general, rather negative, especially on organizing a suitable patient registration system, diet therapy, and the duration of drug therapy before check-up.

None of the variables in the regression analysis had an independent effect on the results.

Barriers to working according the guidelines. Many barriers were brought up by the GPs at the end of the intervention period. Professional-related barriers in the area of knowledge or attitude (predisposing factors) were: a lack of priority for prevention ("I just don't think of case finding"), the time-consuming nature of preventive procedures, the trouble of repeating the cholesterol test three times, hesitation to intervene in a patient's lifestyle, and doubt about the cost-effectiveness of cholesterol intervention. Professional-related barriers in the area of skills (enabling factors) were: difficulties to change practice routines, and feeling of incompetence in guiding patients for diet therapy. Other barriers were not directly related to the professional (reinforcing factors): the complexity of the guideline algorithm, practical problems in monitoring the risk profile, difficulties to change both practice routines and lifestyle for the patient ("diet therapy is frustrating, both for the patient and the GP"), patients actively demanding cholesterol testing ("I'm a doctor, not a negotiator"), interference by cardiologists'/internists' cholesterol management which deviates from the guidelines, and lack of cooperation with these specialists.

TABLE 2. PROPORTION OF GENERAL PRACTITIONERS REGARDING A GUIDELINE TOPIC AS FEASIBLE. (ANSWER CATEGORIES; FEASIBLE = 1, NOT FEASIBLE = 0).

	baseline		follow-up		
	I-group	C-group	I-group	C-group	
Case finding					
performing selective case finding	0.80	0.53	0.80	0.67	
indications for testing	0.78	0.80	0.80	0.80	
suitable patient registration system	0.25	0.25	0.38	0.31	
advising to cease smoking first	0.38	0.33	0.50	0.31*	
Diagnosis					
amount of tests for diagnosis	0.56	0.38	0.75	0.44#	
supplementary lab-exam on suspician only	0.69	0.38#	0.60	0.60	
referring in case of familial hypercholesterolaemia	0.56	0.44	0.56	0.44	
Diet therapy					
cut-off point for diet treatment	0.19	0.38	0.25	0.44	
starting with diet therapy (before drugs)	0.44	0.75#	0.56	0.63	
using specified patient education material	0.33	0.69	0.38	0.69	
continuing diet for another 6 mths	0.25	0.63*	0.63	0.50	**
6 mths diet therapy before check-up	0.19	0.25	0.38	0.25	
6-12 mths diet before considering drugs	0.13	0.06	0.19	0.13	
Drug therapy					
considering drugs after unsuccessful diet	0.50	0.64	0.81	0.64	
cut-off point for drug treatment	0.60	0.87	0.80	0.87	
duration of therapy before check-up	0.06	0.00	0.19	0.13	
target value for treatment	0.63	0.47	0.27	0.40	

*/** $p<0.05$ on difference between groups/ on pre-post differences between groups
#/## $p<0.10$ on difference between groups/ on pre-post differences between groups

During the intervention period on average 24 (SD 15.4) cholesterol consultations were registered per GP. Nearly half of these contacts (47%) were related to former cholesterol diagnosis or therapy. A case finding situation existed in 25% of the contacts. The cholesterol topic was the main reason for encounter in nine percent of the contacts. Table 3 reports

on the general practitioners' awareness of risk factors and non-pharmacological therapies. GPs' awareness of their patients' risk factors is high for CHD in history, hypertension and diabetes, but much lower for family-related factors like familial hyperlipidaemia (Table 3). In 290 (75%) contacts a cholesterol test was ordered, which was the patient's initiative in 22% of the cases. Giving diet advice and provision of leaflets was done rather often, in contrast to supporting/guiding a patient during the diet therapy.

TABLE 3. FREQUENCIES OF OCCURRENCE OF THE SEVERAL GUIDELINE TOPICS ON CONTACT LEVEL, REGISTERED DURING THE INTERVENTION PERIOD. (16 GPs, 385 CONSULTATIONS, MIN. 4, MAX. 51 PER GP).

	number of consultations	(%)
The GP knows about presence/absence of the following risk factors:		
- coronary heart disease in history	345	(90)
- hypertension	345	(90)
- diabetes mellitus	337	(88)
- xanthoma	277	(72)
- xanthelasmata/arcus lipoides < 40 years	276	(72)
- CHD in siblings or parents < 60 years	256	(66)
- lipaemic serum	247	(64)
- familial hyperlipidaemia in the family	180	(47)
Non-pharmacological cholesterol-lowering/cholesterol-related therapy		
- cholesterol-lowering diet advice	175	(46)
- patient education leaflet on cholesterol-lowering diet	117	(30)
- advice to lose weight	48	(13)
- stop smoking advice	46	(12)
- referral to dietician	24	(6)
- supporting/guiding the patient during the diet therapy	12	(3)

Discussion

Although there was an immediate effect of the intervention on GPs' knowledge of the cholesterol guidelines, it did not result in a relevant improvement at follow-up. In fact a remarkable loss in knowledge was shown already three months after the intervention had stopped. There was little effect on GPs' attitude towards the guidelines; agreement on the main topics of the guidelines was already rather high at baseline and low agreement at baseline remained low at follow-up for most items. GPs' opinion about feasibility of the guidelines in daily practice was in general rather low, and the intervention did not have a relevant impact on this opinion. Many barriers to change were mentioned for predisposing, enabling and reinforcing conditions. The large inter-doctor variation in cholesterol consultations, the patient's initiative in 22% of cholesterol testing, and the low frequency of guidance of diet therapy are empirical findings consistent with the barriers mentioned.

A lack of power in the study might have left clinically relevant changes in attitude undetected. Still, only one of the non-significant improvements in the intervention group approximates a low p-value ($P<0.10$) during follow-up and none of the comparisons does

so in pre-post difference between the groups. There might be a tendency towards improvement in the intervention group, but the quantity of the improvement is generally low. On the other hand, the few statistical differences might be caused by coincidence, given the fact that over 20 comparisons were analysed. Given these considerations, it is still not very likely that there was a strong effect. The strength of the study is the absence of self-selection bias guaranteed by the random sampling procedure. We also feel that the combination of quantitative and qualitative study designs enriches and deepens the results. The group of participating GPs is probably not representative in motivation for cholesterol-related practice guidelines because of self-selection of the GPs during the recruitment period. This means, though, that barriers to change experienced by this group of motivated GPs are certainly generalisable to the Dutch GPs.

Why did the implementation of the guidelines with such an intense programme for improvement not show an effect on basic requirements for performance? Apparently there is more to implementation of practice guidelines than the behaviour change theories deal with. Although properly developed guidelines can change clinical practice[18], the effect seems to be more promising with specific implementation strategies. It might be a prerequisite for successful implementation of guidelines with a controversial character that the GPs themselves internalise the guidelines in their own localised consensus procedure[14]. Considering the large number of barriers to change it is very likely that the guidelines would have been less complex after internalisation in a local consensus procedure.

The preventive character of the cholesterol topic might be another explanation. Nearly all or at least a majority of American GPs[19 20 21], Canadian GPs[22], and Swedish GPs[23] regarded CHD prevention as an important task. Despite this kind of belief in preventive care actual performance on screening for risk factors[24] or on dietary and drug treatment[25] is low. Physicians preventive care philosophies diverge in intensity and this influences their preventive performance[26]. The role and responsibilities of the GP in the field of prevention are disputed by others. Doctors are educated and prepared for investigating symptomatic patients and caring and curing the sick, rather than for keeping the healthy ones healthy[27]. Preventive medicine may disturb this function. Still GPs are willing to embrace prevention because they experience a feeling of personal reponsibility for the patient with myocardial infarction whose pre-existent hypercholesterolaemia had been unmeasured and uncontrolled[28 29]. But it becomes more and more clear that a systematic and supportive public health approach to professional, patient and organisation related barriers to the delivery of preventive services is needed[30 31 32].

And what about external influences on the GPs? The doubling of cholesterol testing during the last ten years (chapter 4) might suggest that external influences, such as for example the demanding patient or marketing activities of drug companies, are playing a major role in the cholesterol screening activities of Dutch GPs. Furthermore, the guidelines might not be good enough[33]. While many GPs believe that good practice is not always necessarily based on scientific evidence[34], the scientific validity of the guidelines has not gone unquestioned and cholesterol guidelines have been contradictory throughout the

years. The ongoing debate about which high-risk groups benefit most by cholesterol screening seems to need clarification by the GP. A higher level of evidence might be needed, accompanied by descriptions of the strength of the evidence, as well as information on cost-effectiveness in the primary health care setting, to convince GPs of the importance of certain guidelines[35]. At least guidelines should be user-friendly, which, according to the GPs, is not the case with the cholesterol guidelines.

Overall it can be concluded that the programme for improvement had hardly any relevant impact on basic requirements for working according to the guidelines. It may have been too early for promoting implementation of cholesterol guidelines in general practice, due to the controversial and preventive character of the guidelines. Much attention should be given during the process of development of guidelines to both the scientific validity of the guidelines and their feasibility in daily practice, where the feasibility is directly influenced by existing conditions for delivery of preventive services.

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The evidence base of the guidelines

The effectiveness of cholesterol-lowering interventions in general practice is examined in the format of a systematic review of randomised controlled trials on cholesterol-lowering interventions (chapter 7). The methodological quality of the trials was assessed and the results were quantitatively pooled. This review was executed during the project time and therefore only trials published before 1994 were included. Because important trials were published since then, a summary of the results of recent trials is given in the update section at the end of chapter 7. In chapter 8 studies on cost-effectiveness of cholesterol-lowering interventions are reviewed systematically, and the implications of the methods used in these evaluations for the general practice setting is appraised.

Chapter 7

Effectiveness of cholesterol-lowering interventions in general practice. A meta-analysis of randomised controlled trials.

Abstract

Objectives - To determine the effects of cholesterol lowering on mortality and morbidity.
Design - Meta-analysis of results of 46 randomised controlled trials of cholesterol-lowering treatments, with subgroup-analyses on relevant variables like the methodological quality of the individual trials. Trials published before 1994 were included. These included 132,296 patients without coronary heart disease (CHD), and 30,515 patients with CHD.
Main outcome measures - Total and cause-specific mortality, coronary heart disease morbidity.
Results - Cholesterol lowering has a favourable effect on the occurrence of the first non-fatal myocardial infarction (primary prevention) for men (OR 0.86 (0.75-0.99)), whereas the pooled effect in men with pre-existing CHD (secondary prevention) is non-significant and heterogeneous. The pooled odds ratio on total deaths, for the better than average qualified studies, is 1.02 (0.95-1.08) for primary prevention, and 0.93 (0.85-1.02) for secondary prevention. Drug-mediated primary prevention has an adverse effect on total mortality (OR 1.19 (1.01-1.39)). Secondary prevention seems rewarding in patients with serum cholesterol lower than 6.5 mmol/l (OR on total deaths 0.76 (0.63-0.91)).
Conclusions - No conclusions can be drawn for women, older and younger men, and morbidity in general. Despite a decrease of non-fatal myocardial infarction in men, and despite methodological quality, there is no effect of cholesterol lowering on total mortality for middle-aged men in primary prevention. Secondary prevention seems rewarding for the subgroup of patients with relatively low serum cholesterol. Being symptomatic for CHD rather than being hypercholesterolaemic seems to be an important predictor for the benefit of cholesterol lowering.

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Introduction

The last decade has seen an increasing number of publications on effects of cholesterol reduction, as well as different interpretations of the published results. Meanwhile the cholesterol topic is still controversial[1 2 3], and there is no consensus in literature as to a preferred screening strategy in general practice[4]. Despite continuing discussion, there is a need for guidelines for the practitioner. Systematic reviewing of published papers on the effectiveness on cholesterol lowering is an accepted approach in assessing the evidence that is available for the development of practice guidelines.

Clearly, completeness in data is a prerequisite for meta-analysis. Completeness in data refers to the number of trials included, as well as the careful check of all trials on both mortality and morbidity data, for men and women separately, including post-trial follow-up data. Total mortality was used as primary endpoint because it provides more accurate reflection of overall effectiveness than disease-specific measures, and there is no ambiguity in measuring this endpoint. Other endpoints of interest were CHD mortality/morbidity and other mortality/morbidity (caused by other vascular diseases, cancer, causes not related to illness, other causes). Although morbidity data are more biased in measuring effect, reduction of morbidity without a net effect on mortality can be of importance in terms of quality of life gains.The methodological quality of clinical trials varies and poor quality studies are more likely to have biases in estimating outcome. When poorer quality studies are combined with studies of higher quality, the estimate of the overall treatment effectiveness may have a reduced validity and precision and added variability[5].

From a primary care viewpoint we were interested in possible differences in effectiveness of cholesterol lowering in certain subgroups like primary care patients (ambulatory/non-referred) compared to hospitalised (non-ambulatory/referred) patients[6].

The objectives of this study were: to assess the overall effect on men and women of reduction of serum cholesterol in RCTs of cholesterol intervention, as well as the effect of different types of intervention; to assess the influence of methodological quality on meta-analysis results; to assess the effects in important subgroups, e.g. subgroups defined by setting; to assess the long-term effect of cholesterol reduction.

Methods

Inclusion criteria

Only published randomised controlled trials with designed cholesterol lowering, and at least total mortality or coronary heart disease (CHD) as clinical endpoints, were included. Randomisation was the only quality criterion used to limit the initial data set. All interventions, those currently used, as well as those not currently used, e.g. oestrogen treatment, were considered.

Retrieval of the trials

Eligible trials were located using four approaches: 1) A MEDLINE search of all studies published between 1965 and 1994. Medical subject heading terms used for key and text words included clinical research/clinical trials/randomized controlled trials/random allocation/, cholesterol, human, heart/coronary/mortality/cardiovascular/myocard. In searching for RCTs in Medline we adjusted for the different keywords that were used during the years for 'randomized controlled studies'. 2) A bibliographic review of each trial identified (checking all the references) was carried out. 3) A review of references and reported data of other meta-analyses on this subject, followed by personal communication with the researchers if necessary. 4) A request to relevant pharmaceutical companies to check their literature files and search for trials with the newest drugs.

TABLE 1. CRITERIA FOR QUALITY ASSESSMENT OF CHOLESTEROL INTERVENTION TRIALS.

Comparability of groups		score
A1	- randomisation procedure central and well described	8
	- randomisation procedure decentral and well described	5
A2	- not checked for prognostic differences between the groups	-5
A3	- groups are prognostic comparable (concerning the risk factors for CHD)	5
A4	- > 5% drop outs (Ndropout = [(Nrandom - Nwithdrawn)/Nrandom] x 100%)	-8
A5	- drop outs are well described (with reason for dropout)	3
A6	- all randomised patients are described in the results	-5
A7	- intention-to-treat analysis	8
Comparability of measurement of outcome:		
B1	- patients blinded	6
B2	- patients checked for blinding	1
B3	- therapists blinded	5
B4	- outcome measurement blinded*	5
B5	- placebo present	2
B6	- placebo well described and adequate (indistinguishable from the experimental intervention)	2
B7	- outcome measures well described	5
Miscellaneous:		
C1	- > 4000 (primary)/ > 1500 (secondary) persons per group**	15
	- 2000 - 4000 (primary)/ 750 - 1500 (secondary) persons per group	7
C2	- interventions standardised and well described	3
C3	- interventions controlled well	2
C4	- compliance checked	3
C5	- unsuspected, adverse effects actively investigated	3
C6	- mean follow-up: > 10 years (primary)/ > 4 years (secondary)	12
	- mean follow-up: 6-10 years (primary)/ 3-4 years (secondary)	7
	- mean follow-up: 3-5 years (primary)/ 1-2 years (secondary)	2
	- mean follow-up: < 1 year (primary)/ < ½ year (secondary)	-5
C7	- adequate statistical procedures	3
C8	- multivariate regression analysis	2
C9	- total mortality as outcome measure	7
		100

* the evaluator can be the patient, the therapist, or an external evaluator

** estimating the sample sizes: α=0.05, ß=0.10, p1=10% CHD, p2=8% CHD (primary); p1=30% CHD, p2=25% CHD (secondary)[7]

Quality assessment of the included trials

The methodological quality of the trials was assessed using predefined weighted criteria (Table 1), which were based on existing criteria[8 9]. A trial could score from 0 to 100 points. Each trial was judged by three experienced GP researchers (AK, JS, VK). If available, separate publications on the methods of the trials were used to inform the quality assessors. The judges were blinded for the weight of each criterion, the journal in which the trial was published, the name of the trial, the results of the trial, as well as geographical and time indications. After scoring each trial independently, the judges had to reach consensus by discussion.

The methods of the trials were judged solely on what was explicitly documented about the research methods in the article(s) published about a study. A criterion could not be scored positively on the impression alone that research was properly performed. For example, just declaring that the study groups were comparable at entry is not sufficient; the data underlying this statement had to be reported to score the criterion on comparability of groups positively. The results on quality scoring was tested on systematic difference between primary and secondary prevention trials using the Mann-Whitney U test.

Quantitative pooling

The overall estimate of the treatment effect was obtained by computing the odds ratio (OR) across all the studies[10], using the Mantel-Haenszel method for combining data from 2x2 tables, and, for computational reasons, Cornfield's confidence limits as the best approximation to the exact limits[11]. Data were analysed following the intention-to-treat principle.

A test for heterogeneity by chi^2-testing was used to evaluate the homogeneity of treatment effects across studies[12]. A finding of significant heterogeneity indicates that the variation in treatment effect (odds ratios) among studies exceeds that expected from random variation, possibly due to differences in the interventions, study samples, or designs. The treatment effect was explored for different types of intervention: primary and secondary prevention trials, diet and drug trials, unifactorial and multifactorial trials, each with separate analyses for men and women. The influence of quality of the trials on the pooled estimates was tested using a forward stepwise linear regression model. The dependent variable was the relative risk and the independent variables were quality sumscore of the trial, but also separate quality characteristics like intention-to-treat analysis, blind outcome validation, and mean follow-up time.

This model was also applied to test the influence on the pooled estimates of other important subgroup variables, like setting (ambulatory patients/hospitalised patients), percentage of males, percentage CHD at baseline, mean baseline serum cholesterol, and percentage change in cholesterol between intervention and control groups. According to the results of the regression analysis, odds ratios were pooled in strata with the following characteristics; quality sumscores above mean quality score, the best six trials, blind outcome validation, and ambulatory patients only. The full effect of reduction in risk is

achieved over five years[13]. Therefore trials with a duration longer than five years were taken as a separate stratum. Mean baseline cholesterol higher or lower than 6.5 mmol/l was also taken as a stratum because 6.5 mmol/l is the cutoff point for intervention according to the Dutch GP guidelines. Available data on post-trial follow-up experience were pooled to explore the long-term effect of cholesterol reduction.

Results

Description of studies and populations included

A total of 46 trials were included in the meta-analysis. Fifteen of these involved primary prevention: two unifactorial diet studies, seven unifactorial drug studies, and six multifactorial studies. The remaining 31 trials involved secondary prevention: nine unifactorial diet studies, 18 unifactorial drug studies, one unifactorial surgical study, and three multifactorial studies.

The size of the trials was variable, ranging from 57,460 patients in a multifactorial primary prevention trial, to 48 patients in a multifactorial secondary prevention trial. The mean follow-up time varied from nearly one to 10 years, with just over half of the trials (26/46) having a follow-up of at least 3 years. The main characteristics of the trials are summarised in appendix 3. In general, the secondary preventive trials did not require a minimum level of serum cholesterol as inclusion criterion, and thus they assessed the systematic application of lipid lowering intervention following myocardial infarction (MI) rather than the effects of treatment of hypercholesterolaemia in post-MI patients.

In total, data on 132,296 people without CHD, and 30,515 people with CHD were analysed. Only 5 of the 15 primary, and 19 of the 31 secondary prevention studies included women. Only in 6 of these studies were results reported for men and women separately. The patient samples are mainly restricted to middle-aged persons. The mean age for the populations under study was comparable for primary and secondary prevention studies. The results of the individual trials are described in table 2. The odds ratios for the individual trials on total deaths and coronary deaths are given. Especially the odds ratios on coronary deaths appear to diverse considerably.

Quality assessment

It took the judges on average 16.2 hours to score the 46 trials. There was immediate consensus on about two-thirds of the criteria. It took 16.5 hours of discussion to reach total consensus. Only 14 of the 46 trials scored higher than 50 points (Table 2). The primary prevention trials had a significantly ($p=0.01$) higher mean quality score (49.9, SD 18.2) than the secondary prevention trials (35.6, SD 17.5). The detailed results on methodological quality are presented in appendix 4.

TABLE 2. OVERVIEW OF THE RESULTS OF THE TRIALS IN INTERVENTION GROUP/CONTROL GROUP

	total deaths	coronary deaths	non-fatal MI	total deaths OR (exact CI)	CHD deaths OR (exact CI)	quality sum score
Primary prevention trials						
diet						
Dayton 69[14 15 16]	174/177	41/50	13/21	0.96 (0.73-1.28)	0.80 (0.50-1.26)	53
Frantz 89[17]	269/248	61/54	-	1.08 (0.90-1.30)	1.12 (0.77-1.66)	43
drugs						
LRC 84[18 19]	68/71	30/38	130/158	0.95 (0.67-1.36)	0.78 (0.47-1.30)	77
Frick 87[20 21 22 23 24]	45/42	14/19	45/71	1.06 (0.68-1.67)	0.73 (0.34-1.53)	70
Oliver 78[25 26 27]	236/181	91/77	-	1.31 (1.07-1.60)	1.18 (0.86-1.62)	60
Bradford 91[***28 29 30 31]	33/3	28/3	37/18	2.78 (0.87-14.25)	2.36 (0.73-12.2)	44
Dorr 78[***32]	37/48	19/31	-	0.75 (0.47-1.19)	0.60 (0.32-1.10)	41
McCaughan 81[***33]	2/3	2/2	-	0.21 (0.02-1.96)	0.33 (0.02-4.74)	29
Gross 73[34]	1/2	1/0	-	0.62 (0.01-12.64)	-	5
multifactorial						
MRFIT 82[35 36 37 38]	265/260	115/124	171/165	1.02 (0.85-1.22)	0.93 (0.71-1.21)	73
Hjermann 81[39 40]	16/24	6/14	13/22	0.68 (0.34-1.36)	0.44 (0.14-1.23)	58
WHO 86[41 42 43]	1325/1186	428/398	505/505#	0.99 (0.91-1.07)	-	58
Wilhelmsen 86[44 45]	-	-	501/489	-	-	55
Appels 89[46 47]	14/17	1/11	8/12	0.81 (0.36-1.82)	0.09 (0.00-0.61)	51
Miettinen 85[48 49]	10/5	4/1	15/8	2.01 (0.62-7.54)	4.00 (0.39-198)	26
Secondary prevention trials						
diet						
Singh 92[***50]	28/51	25/45	30/48	0.47 (0.27-0.81)	0.49 (0.27-0.86)	54
Leren 70[***51 52]	41/55	37/50	-	0.68 (0.42-1.11)	0.68 (0.41-1.13)	49
Burr 89[***53 54]	111/113	97/97	-	0.98 (0.73-1.30)	1.00 (0.73-1.36)	47
MRC Ball 65[55]	20/24	17/20	10/7	0.83 (0.41-1.68)	0.86 (0.40-1.82)	40
Reis 89[56]	-	-	7/0	-	-	39
Woodhill 78[* ***57]	39/28	37/24	-	1.60 (0.92-2.81)	1.78 (1.00-3.24)	37
Morrison 69[58 59]	7/15	6/13	-	0.38 (0.12-1.13)	0.39 (0.11-1.24)	32
MRC Morris 68[***60]	29/32	25/26	20/26	0.86 (0.48-1.55)	1.02 (0.54-1.92)	28
Rose 65[61]	-	8/1	13/5	-	4.29 (0.52-200.5)	10
drugs						
Canner 86[62 63 64 65 66 67]	219/525	162/410	103/242	1.07 (0.89-1.28)	1.00 (0.82-1.22)	86
	91/193	67/133	56/76	1.19 (0.91-1.55)	1.27 (0.93-1.73)	
	160/339	119/274	78/175	1.25 (1.02-1.54)	1.13 (0.89-1.43)	
	288/723	240/632	114/304	1.01 (0.86-1.19)	0.95 (0.80-1.13)	
	277/723	238/632	84/304	0.94 (0.80-1.11)	0.92 (0.78-1.09)	
Frick 93[68]	19/12	17/8	18/16	1.65 (0.75-3.80)	2.23 (0.90-6.07)	71
Brensike 84[* ***69 70]	5/7	5/6	3/5	0.71 (0.17-2.73)	0.83 (0.19-3.46)	55
Stamler 63[71]	37/40	-	-	0.62 (0.35-1.08)	-	48
Cashin 90[72 73 74]	1/2	1/2	4/10	0.50 (0.01-9.69)	0.50 (0.01-9.69)	42
Brown 90[75]	0/0	0/0	0/0	-	-	41
	1/0	1/0	1/0	-	-	
Acheson 72[**76]	23/20	13/5	-	1.34 (0.55-3.26)	3.25 (0.97-12.82)	37
Carlson 72[77]	61/82	47/73	35/50	0.66 (0.44-0.99)	0.56 (0.36-0.87)	33
Newcastle 71[***78 79]	31/52	27/48	20/38	0.58 (0.34-0.96)	0.53 (0.31-0.91)	33
Oliver 61[80]	17/12	13/10	5/8	1.62 (0.63-4.32)	1.40 (0.50-4.04)	29

TABLE 2. CONTINUED.

	total deaths	coronary deaths	non-fatal MI	total deaths OR (exact CI)	CHD deaths OR (exact CI)	quality sum score
secondary prevention trials, continued						
Bellandi 93[81]	1/1	-	1/3#	0.96 (0.01-76.81)	-	28
Sahni 91[*82 83]	3/4	1/3	3/4	0.73 (0.10-4.49)	0.32 (0.01-4.12)	26
Scottish Soc 71[84 79]	38/42	30/29	30/37	0.92 (0.56-1.53)	1.08 (0.60-1.93)	25
Schoch 68[85 86]	27/27	25/23	26/19	1.02 (0.54-1.92)	1.12 (0.58-2.20)	22
	10/27	8/23	12/19	0.67 (0.27-1.55)	0.63 (0.23-1.57)	
	15/27	13/23	12/19	1.04 (0.48-2.20)	1.06 (0.46-2.35)	
	13/27	10/23	11/19	1.03 (0.45-2.27)	0.92 (0.36-2.16)	
	16/27	15/23	9/19	1.32 (0.61-2.79)	1.47 (0.66-3.22)	
Watts 92[87]	0/3	0/3	1/2#	0.00 (0.00-2.37)	0.00 (0.00-2.37)	22
	1/3	1/3	1/2	0.32 (0.01-4.21)	0.32 (0.01-4.21)	
Harrold 69[88]	0/3	0/2	-	0.00 (0.00-2.62)	0.00 (0.00-5.48)	18
Kane 90[89]	0/1	0/0	0/1	0.00 (0.00-39.81)	-	18
Marmorston 62[90]	70/38	62/35	-	0.93 (0.58-1.52)	0.89 (0.54-1.48)	12
surgical						
Buchwald 90[91 92 93 94]	49/62	32/44	59/94	0.75 (0.49-1.15)	0.70 (0.42-1.15)	61
multifactorial						
Kallio 79[95]	41/56	35/55	34/21	0.65 (0.40-1.07)	0.55 (0.33-0.91)	31
Schuler 92[96]	2/0	2/0	0/3	-	-	18
Ornish 90[97]	1/0	1/0	-	-	-	13

* unpublished data collected by Davey Smith, 1993 (Davey Smith G, Song F, Sheldon TA. Cholesterol lowering and mortality: the importance of considering initial level of risk. BMJ 1993;306:367-73)

** unpublished data collected by Law, 1994 (Law MR, Thompson SG, Wald NJ. Assessing possible hazards of reducing serum cholesterol. BMJ 1994;308:373-9)

\# no information available on withdrawals

Quantitative pooling

Mortality. The only one pooled odds ratio on total mortality that reaches significance level (diet studies in secondary prevention) lacks homogeneity, so no conclusive results can be reported (Table 3). Heterogeneity of the pooled odds ratios on total mortality is mainly seen in secondary prevention. Drug-mediated cholesterol lowering in primary prevention trials tends to have an adverse effect although the odds ratio 1.13 is not significant. Drug-mediated secondary prevention studies show no effect on total mortality (OR 1.00), but have a significant adverse effect on circulatory deaths other than coronary causes: pooled OR 1.55 (1.03-2.29) based on 16 studies with 4052 intervention and 7306 control patients. Seven out of 9 pooled odds ratios on coronary deaths show heterogeneity. Analysis of different types of intervention does not relevantly influence the pooled estimates on coronary deaths.

The pooled estimate on total deaths with inclusion of men only is 1.02 (95% CI 0.97-1.06) based on 37 studies with 59796 intervention and 64894 control patients. Occurrence of heterogeneity decreases from 11 to only 3 times with the odds ratios of analyses on men only. The pooled OR on total death based on data of women only is 1.13 (0.88-1.43), estimated by pooling 3 studies with 2991 intervention and 2935 control patients.

TABLE 3. EFFECT OF DIFFERENT TYPES OF INTERVENTIONS ON POOLED ODDS RATIOS ON TOTAL DEATHS AND CORONARY DEATHS OF THE 46 TRIALS, BOTH MEN AND WOMEN INCLUDED. THE TOTAL NUMBER OF TREATMENT COMPARISONS AVAILABLE FOR POOLING IS 56. N= NUMBER OF STUDIES.

	TOTAL DEATHS			CORONARY DEATHS		
	OR (95% CI)	n° of pat. (I/C)	n =	OR (95% CI)	n° of pat. (I/C)	n=
all studies combined	1.00 (0.95-1.04)*	71257/71255	53	0.94 (0.89-1.00)*	71107/71116	52
primary prevention	1.02 (0.96-1.08)	60424/51857	14	0.94 (0.85-1.03)*	60424/51857	14
- unifactorial studies	1.09 (0.98-1.21)	22096/17014	9	0.97 (0.81-1.15)	22096/17041	9
- diet-studies	1.00 (0.94-1.07)	42486/38975	5	0.94 (0.84-1.05)	42486/38975	5
- drug-studies	1.13 (0.98-1.31)	17938/12882	9	0.93 (0.75-1.15)*	17938/12882	9
secondary prevention	0.97 (0.90-1.03)*	10833/19398	39	0.94 (0.88-1.01)*	10683/19259	38
- unifactorial studies	0.97 (0.91-1.04)*	10561/19134	36	0.95 (0.89-1.03)*	10411/18995	35
- diet-studies	0.83 (0.70-0.98)*	2300/2302	10	0.86 (0.72-1.02)*	2354/2328	11
- drug-studies	1.00 (0.93-1.08)	8112/16679	28	0.97 (0.90-1.05)*	7908/16514	26

* test for heterogeneity: $p<0.05$

Separate analysis using quality criteria does not improve the effect of cholesterol lowering intervention (Table 4). Instead, a significant adverse effect is shown for primary prevention drug studies. Analysis of trials with blind assessment of outcome also tends towards decrease in effectiveness, except for secondary diet studies. Analysis of the best six trials did not change these results. Separate analysis of trials with longer duration ($\geq$ 5 years) influenced the results for primary prevention studies, again showing decrease in effect.

TABLE 4. EFFECT OF QUALITY AND OTHER IMPORTANT VARIABLES ON POOLED ODDS RATIOS ON TOTAL DEATHS OF THE 46 TRIALS, BOTH MEN AND WOMEN INCLUDED. N= NUMBER OF STUDIES.

	OR (95% CI)	n° of patients (I/C)	n =
primary prevention studies			
quality $\geq$ 50	1.02 (0.95-1.08)	47429/43880	8
- drug-studies only	1.19 (1.01-1.39)	9289/9225	3
blind assessment of outcome	1.07 (0.98-1.17)	29740/24690	12
trial duration $\geq$ 5 years	1.09 (0.97-1.22)	17128/17097	7
studies with ambulatory patients only	1.02 (0.96-1.09)	54310/45790	11
baseline cholesterol $\geq$ 6.5 mmol/l	0.99 (0.87-1.13)	19444/14456	9
baseline cholesterol < 6.5 mmol/l	1.03 (0.96-1.10)	40785/37205	4
- unifactorial only	1.14 (1.01-1.28)	10296/10234	3
secondary prevention studies			
quality $\geq$ 36	0.93 (0.85-1.02)	5195/8543	15
- drug-studies only	0.97 (0.87-1.08)	2995/6332	9
blind assessment of outcome, diet only	0.83 (0.67-1.03)	1551/1545	4
blind assessment of outcome, drugs only	0.96 (0.86-1.06)	3377/6772	11
trial duration $\geq$ 5 years	0.97 (0.88-1.08)	3499/6875	8
studies with ambulatory patients only	0.79 (0.53-1.16)	642/626	3
baseline cholesterol $\geq$ 6.5 mmol/l	1.01 (0.94-1.08)	8957/17420	23
baseline cholesterol < 6.5 mmol/l	0.76 (0.63-0.91)	1561/1798	14

Subgroup analysis on ambulatory patients only does not change the pooled OR of total mortality for primary prevention studies (Table 4). However, the subgroup analysis on ambulatory patients only in secondary prevention studies results in a positive but non-significant effect on total mortality. In primary prevention, patients with an average baseline cholesterol lower than 6.5 mmol/l seem to benefit less from cholesterol lowering, especially in unifactorial studies, while such patients in secondary prevention seem to benefit significantly from cholesterol lowering. Again, separate analysis on men only did, apart from decreasing heterogeneity, not change these results.

Data on post-trial follow-up were available for seven primary prevention trials (mean post follow-up 4.9 years), and seven secondary prevention trials (mean post follow-up 7.9 years) (Table 5). Primary prevention studies do not show long-term effect on total mortality, whereas secondary prevention studies seem to, but lack homogeneity. In contrast to cancer deaths (OR in-trial 1.13 (0.96-1.34) based on 39 trials with 36578 intervention and 34777 control patients, OR post-trial 0.90 (0.82-1.00)), deaths not related to illness did not change during post follow-up (OR in-trial 1.19 (0.93-1.53) based on 38 trials with 36299 intervention and 34501 control patients, OR post-trial 1.21 (0.84-1.74)).

TABLE 5. POOLED ODDS RATIOS ON MORTALITY, POST-TRIAL FOLLOW-UP DATA, BOTH MEN AND WOMEN INCLUDED.

	OR (95% CI)	n° of patients (I/C)	n =
total deaths	0.96 (0.91-1.00)*	32718/41113	14
- primary prevention studies only	0.99 (0.93-1.05)	26937/26912	7
- secondary prevention studies only	0.92 (0.87-0.98)*	5781/14201	7
coronary deaths	0.99 (0.93-1.04)	32668/41063	13
other circulatory deaths	0.91 (0.76-1.10)	19850/24864	9
cancer deaths	0.90 (0.82-1.00)	31089/35933	12
deaths not related to illness	1.21 (0.84-1.74)	19361/22685	9
other/unknown deaths	0.95 (0.78-1.15)	18543/21869	7

* test for heterogeneity: $p<0.05$

Morbidity. Except for data on non-fatal myocardial infarctions (MI), extraction of morbidity data was not very rewarding. Only one trial presented data on total morbidity, and for the greater part differentiation in various types of morbidity is subject to caveats (complete data available on request). Pooled ORs on non-fatal MI show much heterogeneity, which is again reduced in analysis on men only (Table 6). Primary preventive unifactorial studies, both men and women included, result in a significant OR in favour of cholesterol lowering, as well as primary prevention studies for men only.

TABLE 6. POOLED ODDS RATIOS ON NON-FATAL MI OF THE 46 TRIALS, SUBGROUP ANALYSES.

	MEN AND WOMEN OR (95% CI)	n° of pat.(I/C)	n =	MEN ONLY OR (95% CI)	n° of pat.(I/C)	n =
all studies combined	0.93 (0.87-1.00)*	37478/41205	37	0.91 (0.84-0.99)*	19598/28318	27
primary prevention	0.93 (0.85-1.02)*	28807/23897	9	0.86 (0.75-0.99)	12221/12223	7
- unifactorial studies	0.71 (0.59-0.86)	10964/6014	4	0.73 (0.60-0.90)	4382/4351	3
- multifactorial studies	1.02 (0.92-1.14)	17843/17883	5	1.00 (0.82-1.23)	7839/7872	4
- studies with ambulatory patients	0.94 (0.85-1.03)*	28383/23475	8	0.87 (0.75-1.00)	11797/11801	6
secondary prevention	0.94 (0.85-1.03)*	8671/17308	28	0.94 (0.85-1.04)*	7377/16095	20
- unifactorial studies	0.93 (0.84-1.02)*	8427/17064	26	0.95 (0.85-1.05)*	7321/16038	19
- unifactorial drug-studies	0.96 (0.86-1.06)*	7486/16226	21	0.99 (0.89-1.10)*	6745/15478	16

* test for heterogeneity: $p<0.05$

Discussion

Main results

Although data of 160,000 patients are available now, there is still no clear effect of cholesterol lowering intervention on total mortality in primary prevention. Cholesterol lowering diet in secondary prevention seems effective, but the odds ratio lacks homogeneity. Secondary prevention has a significant adverse effect on circulatory deaths other than coronary causes. Analyses of data on men only does not change the effects, but decreases heterogeneity. On the other hand, cholesterol lowering significantly decreases occurrence of non-fatal MI, but only in primary prevention studies restricted to men.

Evaluation of studies of higher quality does not improve the effect of cholesterol lowering intervention on total mortality, even resulting in a significant adverse effect for primary prevention drug studies. Several drug studies with different cholesterol lowering mechanisms, and even diet studies, have demonstrated the same inverse relationship. Probably, aggressively lowering high serum cholesterol in a relatively short time has adverse effects. Blind assessment of outcome is probably responsible for the influence of quality on effectiveness.

Restriction to ambulatory patients seems to favour cholesterol lowering in secondary prevention. In primary prevention the level of patients' baseline cholesterol does not influence results, whereas in secondary prevention cholesterol lowering in patients with baseline cholesterol below 6.5 mmol/l is beneficial. Thus, being symptomatic for CHD rather than being hypercholesterolaemic, determines whether cholesterol lowering intervention will be beneficial. The amount of difference of actual cholesterol reduction between intervention and control group, as well as a follow-up of at least 5 years did not improve results. On the other hand, secondary prevention seems to be beneficial in the long term.

There are several caveats in knowledge of effectiveness of cholesterol lowering; there is little or no data on women, on men older and younger than middle-age, and on morbidity

other than coronary morbidity. It is not clear whether data based on mainly middle-aged white men can be extrapolated to other subgroups, because important differences in drug responses and risk profiles exist among these subgroups[98-101].

Methodological considerations

Only published RCTs were included. Publication bias occurs if the results from unpublished studies are different from the published ones[102-104]. It especially concerns data of aborted trials, and trials with negative results (submission and editorial bias)[105 106]. It also concerns non-publication of studies with similar results to the published ones because this will influence the strength of the evidence[107]. Unpublished results may, on the other hand, be less reliable, since they have not been found acceptable by peer reviewers[108 109]. For this reason and because retrieval of unpublished trials may take several years, we included published trials only.

In quality scoring, the judges were not able to differentiate between poor quality resulting from deficiencies in the methods of the studies versus deficiencies in the way in which the studies were reported. Given space constraints in most journals, editorial decisions may end up having a major effect on the quality score achieved by a given study[110]. On the other hand, if no points are scored for quality due to insufficient description, this gives false-positive bias if the score on the criterion is expressed in negative points. Quality assessment was probably done in a way comparable to former investigators, who found the same average quality score in 107 primary prevention trials[111].

Some authors advocate application of the random effects method in case of heterogeneity of the pooled result[112]. This method was not used in this study because results of subgroups which we are interestered in were mostly homogeneous, and because this method does not affect the point estimate but generally produces wider confidence intervals for the pooled estimate than fixed effects methods[113]. Heterogeneity may be due to variation in sampling methods resulting in diverse study populations, which may increase generalisability of the results. Heterogeneity of studies may also help to detect an association between study characteristics and outcome[114].

Comparison with literature

Prospective cohort studies may clarify our findings on the unexpected fail of decrease in total mortality to appear. They showed no relation between baseline serum cholesterol and total mortality in women but a U-shaped risk curve in men, with significant adverse trends for deaths due to haemorraghic stroke, cancer, benign liver disease, chronic obstructive lung disease, digestive disease, and trauma[115 116]. Excluding early deaths from the analysis did not change these results. In another study a drop in serum cholesterol level about two years prior to cancer diagnosis was reported, but only in patients with non-localised cancers[117]. The association between serum cholesterol and non-atherosclerotic deaths seems biologically plausible[118]. Except for two studies[119 120], a significant positive relation was reported in men, again not for women[121], of either colon[122], lung[123],

lung and haemopoietic cancers[124], or all-cancer with low serum cholesterol, which attenuated over time (7[125], 12[126 127], 28 years of follow-up[121]), and also persisted after exclusion of early deaths[124].

We found a significant adverse effect of cholesterol reduction on circulatory deaths other than coronary causes in secondary prevention studies. Of non-coronary circulatory deaths haemorraghic stroke was found to relate inversely with serum cholesterol in men in a prospective study[128]. In Japan a significant inverse association was found between serum cholesterol and the incidence of stroke[129].

The non-significant excess deaths not related to illness in primary prevention trials also seem to match, except for two studies[130 131], with data of cohort studies[126 132 133]. This negative relation was stronger during the first years of follow-up, which supports the hypothesis that lowering cholesterol instead of a history of low cholesterol increases risk of violent death. Several studies report an association between low serum cholesterol level and aggression or depression in monkeys[134], men[135-141], and women[142 143]. Recently depressive symptoms in hypercholesterolaemic patients treated with pravastatin[144], and with simvastatin[145] were reported. There are several hypotheses to clarify the association between low serum cholesterol and deaths not related to illness: 1) It is due to chance[146]; 2) Low serum cholesterol (or lowering serum cholesterol[147]) influences brain membrane cholesterol thereby decreasing the number of serotonin receptors, which ultimately affect behaviour[148 149]; 3) A common factor underlies both depression and low serum cholesterol (weight loss consequent upon depression or upon illness, leading to depression)[150]; 4) The 'violent' deaths were often accidental and therefore could have involved an unrecognised cardiac component; 5) Effective prevention of early coronary symptoms causes the subjects to choose a more active life-style, which may predispose to fatal accidents[151].

In contrast with the relation between low cholesterol and deaths from certain causes, which persists even after excluding early deaths, all cause mortality did increase with increasing serum cholesterol in a cohort with persons derived from a working population demonstrating a health selection effect[152]. Factors related to underlying health status, like lower employment grade, disease at baseline, history of recent unexplained weight loss, being widowed[123], malnutrition, infection[153], rather than an independent mortality enhancing effect of low cholesterol, seem to account for the excess risk of death among persons with low cholesterol[154].

Conclusions

No conclusions on the effectiveness of cholesterol lowering are possible on women, older and younger men. Taking methodological quality into account, it can be concluded for middle-aged men that cholesterol lowering has no effect on total mortality in primary prevention, although there seems to be an exchange of coronary deaths for non-atherosclerotic deaths. Drug-mediated primary prevention has an adverse effect on total mortality, and drug-mediated secondary prevention has an adverse effect on circulatory deaths other

than CHD deaths. Secondary prevention seems rewarding in non-hospitalised patients with relatively low serum cholesterol.

Although cholesterol lowering has a favourable effect on the occurrence of non-fatal MI in primary prevention - whereas the pooled effect in secondary prevention is non-significant and heterogeneous - we do not have enough information to conclude about effectiveness on morbidity in general. Availability of results of all unpublished trials and use of random effects methods for quantitative pooling would probably have made the results even more conservative.

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Supplement to chapter 7

Updating the evidence base.

The continuous and presumably never-ending cholesterol discussion can not be ignored. The results of many new trials were published since the time the search activities for chapter 7 were closed. Naturally, most of them focus on the effectiveness of the new generation drugs, the HMG-co-A reductase inhibitors. This update starts with listing the reviews on the effect of cholesterol lowering published during the course of the research activities for chapter 7, followed by those published after chapter 7 was finished. Then, an overview is given of the recently published RCTs including a crude enumeration of their results. A closer look is given of the larger trials that were designed to measure effect on clinical outcome or trials executed on persons without CHD. Finally, the main results of this new evidence will be summarised in the discussion.

Published reviews

During the course of the research activities of chapter 7 at least 20 meta-analyses about effectiveness of cholesterol reduction, analysing results of between 6 to 35 studies each, had already been published[1-21]. They all vary in trial selection, partly in terms of emphasis, and their conclusions have been different. In 1990 Muldoon reported an association between reduction of cholesterol concentrations and trauma deaths, and questioned the benefits of reducing cholesterol concentration in the general population[3]. In 1991 Silberberg concluded that benefits of cholesterol lowering are substantially greater in patients with CHD, the so-called secondary prevention, than in persons without CHD[4]. In 1992, Davey Smith advocated a moratorium on the use of cholesterol lowering drugs in primary prevention[6], and Ravnskov claimed that cholesterol lowering is unlikely to prevent CHD[8]. In 1993, Davey Smith concluded that cholesterol lowering benefits mortality in only a small proportion of patients at very high risk of death from CHD[12]. The results of chapter 7 are in line with the conclusions drawn in the papers of Muldoon, Silberberg and Davey Smith.

The discussion continues with Law in 1994 who claims strong evidence for effectiveness and safety of lowering serum cholesterol[18 19]. Law based his conclusions both on RCTs and prospective studies. We think RCTs are more reliable in this matter, because they are designed to provide unbiased comparisons of outcomes following treatments, and because decreasing cholesterol concentrations can have different biological effects than consistently low concentrations.

Since 1994, by the time the research-activities for chapter 7 were closed, at least another ten meta-analyses have been published. The conclusions in these meta-analyses focus on the effectiveness of the HMG-coA reductase inhibitors, and can be divided in reviews on primary and/or secondary prevention trials with clinical outcomes[22], reviews on regression studies only[23-26], and papers reviewing both types of outcomes[27-32].

The reviews on regression studies concluded that HMG-co-A reductase inhibitors have a positive effect on angiographic outcome. The higher the baseline low density lipoproteins, the greater the improvement in the stenosis. In contrast, neither a low LDL level achieved on treatment nor a large percentage reduction in LDL was related to improvement in lesions[25]. The pooled results provided evidence that cardiovascular events were reduced in patients with CHD[26]. The drug trials reduced total mortality in patients with CHD[28]. A dose-response relation was reported between total mortality and degree of cholesterol reduction adjusting for risk level in the control group and also for treatment type[29]. The effect of cholesterol-lowering interventions was reported as established in patients with CHD[31], but the transferability of the results to real-life patients was put as the critical, unanswered question. Another review reports that number-needed-to-treat analysis supports the clinical benefit of treating hypercholesterolaemia, both in persons with and without known atherosclerosis[30]. Screening on serum cholesterol levels is most likely to be useful when done in populations at high short-term risk for dying of CHD, such as CHD-survivors and middle-aged men with multiple cardiac risk factors[32].

Published RCTs

After the inclusion of trials for chapter 7 was closed, the results of at least 20 new cholesterol-lowering intervention trials were published. Five new trials concerned primarily clinical outcomes. The West of Scotland Coronary Prevention Study (WOSCOPS) investigated the effect of pravastatin in persons without CHD[33 34]. Two trials investigated the effect of simvastatin and pravastatin in persons with CHD: the Scandinavian Simvastatin Survival Study (4S)[35-38], and the Cholesterol and Recurrent Events trial (CARE)[39 40]. Another two trials investigated the effect of lipid lowering in mixed populations: a trial on the effects of lovastatin and niacin[41], and the Pravastatin Multinational Study[42]. The main conclusions of the largest trials (WOSCOPS, 4S, CARE) will be discussed below.

Fourteen new trials concerned primarily angiographical outcomes. The Kuopio Atherosclerosis Prevention Study (KAPS)[43 44] and the Carotid Atherosclerosis Italian Ultrasound Study[45] investigated the effect of pravastatin, and the Asymptomatic Carotid Artery Progression Study (ACAPS)[46 47] investigated the effect of lovastatin on persons without CHD. The results of KAPS and ACAPS, the larger studies, will also be discussed below. The other nine trials investigated the effect of lipid lowering on symptomatic patients: the Multicentre Anti-Atheroma Study (MAAS)[48] (simvastatin slowed progression of coronary atheroslcerosis), the Pravastatin, Lipids and Atherosclerosis in the Carotid arteries study (PLAC I-II)[49-54] (pravastatin reduced reoccurence of coronary events), the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)[55 56] (lovastatin slowed progression of coronary atherosclerosis), the Regression Growth Evaluation Statin Study (REGRESS)[57 58] (pravastain reduced cardiovascular events), the Harvard Atherosclerosis Reversibility Project (HARP)[59 60] (intensive drug treatment of normocholesterolaemic patients had no angiographically measurable benefit on the coronary arteries), the Lovastatin Restenosis

Trial[61] (lovastatin initiated before coronary angioplasty did not prevent or delay the process of restenosis), the Monitored Atherosclerosis Regression Study (MARS)[62 63] (lovastatin slowed the rate of progression in coronary arteries), and two studies on the effect of fish oils on either restenosis[64] or regression[65] (no effects were seen). Two trials investigated the effect of lipid lowering in mixed populations: the Familial Hypercholesterolaemia Regression Study[66] (lipoprotein apheresis was less beneficial in reducing coronary atherosclerosis than simvastatin), and the Probucol Quantitative Regression Swedish trial (PQRST)[67 68] (probucol did not result in significant regression compared to cholestyramine).

One multifactorial intervention trial was published on coronary risk factor modification in patients with CHD; the Stanford Coronary Risk Intervention Project (SCRIP)[69 70] (favourable effect on angiographic and clinical outcomes).

Closer look on relevant trials

The main characteristics and results of relevant trials are described in table 1. The WOSCOPS, KAPS, and ACAPS studies were executed in populations without CHD, the 4S and CARE studies in populations with CHD. The WOSCOPS study was the first primary prevention trial of lipid lowering drug therapy to show a reduction in all-cause mortality, which nearly reached significance (p=.051). The risk of developing CHD of the different populations can be compared by looking at the CHD-incidence in the placebo groups: 7.9 in WOSCOPS in 5 years, 3.4 and 3.5 in KAPS and ACAPS after 3 years, 22.6 and 13.2 in 4S and CARE after 5 years. The net absolute risk reductions on (non)fatal myocardial infarctions were 2.4, 2.1, 2.4, 6.7, and 3.0 respectively, so the higher the populations

TABLE 1. CHARACTERISTICS AND RESULTS OF RELEVANT TRIALS.

	WOSCOPS	KAPS	ACAPS	4S	CARE
intervention treatment/control	pravastatin/ placebo	pravastatin/ placebo	lovastatin/ placebo	simvastatin/ placebo	pravastatin/ placebo
mean duration (yrs)	4.9	3.0	3.0	5.4	5.0
No of patients (tr/con)	3302/3293	224/223	460/459	2221/2223	2081/2078
age-range, mean (yrs)	45-64, 55	42-60, 57	40-79, 62	35-70, 59	21-75, 59
male (%)	100	100	52	81	86
baseline cholesterol	7.0	6.7	7.3	6.8	5.5
symptomatic patients (%)	5 (AP)	7 (MI)	0	100	100
(non)fatal MI	174/248*	3/8	5/14	353/502*	212/274*
(absolute % risk)	(5.5/7.9)	(1.3/3.4)	(1.1/3.5)	(15.9/22.6)	(10.2/13.2)
total deaths	106/135	3/4	1/8	182/256*	180/196
(absolute % risk)	(3.2/4.1)	(1.3/1.8)	(0.2/1.7)	(8.2/11.5)	(8.6/9.4)

* statistically significant, p< .05

CHD risk, the higher the effect of cholesterol lowering. The phenomenon of increased non-coronary mortality in the treated groups seen in previous trials no longer occured. The absolute risk reductions on total death were all in favour of the intervention but much smaller, ranging from 0.5 to 3.3. The risk reduction in the 4S study was independent of baseline cholesterol concentrations and a dose-response relation was lacking. In contrast, the effect of cholesterol lowering in patients with CHD seems far lower in those with a relatively low baseline level of cholesterol (like in CARE) than in patients with hypercholesterolaemia (like in 4S). The 4S and CARE study reported subgroup analyses on women. The same magnitude of effect on coronary events was seen in women as in men in the 4S and CARE study. Nevertheless, no benefit on total mortality was seen in women in the 4S study, the only trial in which data on total deaths were reported for women separatedly.

Discussion

There is growing consensus on the efficacy of cholesterol lowering in patients with CHD. Regression studies concluded positively on the effect of HMG-co-A reductase inhibitors on angiographic outcome. The recent finding that cholesterol lowering reduced total mortality in CHD patients is of great importance in this matter. In short, the effect of cholesterol lowering is reported as established in patients with CHD. The evidence is convincing for the subgroup of middle-aged white men, but the transferability of the results to real-life patients was put as the critical, unanswered question. Surprisingly, the risk reduction in the 4S study was independent of baseline cholesterol concentrations and a dose-response relation was lacking. It was argued that the beneficial effects of simvastatin may be due to non-lipid actions, or that other effects of cholesterol lowering play their role, such as e.g. an improvement in endothelium-dependent vasomotion of the coronary arteries[71]. Such improvement in the local regulation of coronary arterial tone could potentially relieve ischemic symptoms[72]. It is suggested that statins improve hemorheological characteristics involved in coagulation and vasomotion early in the course of therapy[73] [74]. The discrepancy between anatomic change and clinical benefit in the regression studies has led to the concept that the reduction in clicical events is due more to a change in the composition of the plaque, making it less vulnerable to rupture, than to a reduction in the size of the plaque[75].

At the same time there is far less information and more uncertainty on the interpretation of the smaller benefits of cholesterol lowering in persons without CHD. Screening on serum cholesterol levels is most likely to be useful when done in populations at high short-term risk for dying of CHD, such as survivors of myocardial infarction and middle-aged men with multiple cardiac risk factors. It is not clear what exactly is the cutoff point in the level of CHD risk when it is worthwhile to intervene on the cholesterol level. A simple principle seems to come forward; do not treat healthy people, but intervene in persons who are already symptomatic for CHD or are very likely to become ill in short time.

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Chapter 8

Economic evaluation of cholesterol-related interventions in general practice. An appraisal of the evidence.

Abstract

Study objective- To investigate the present knowledge on cost-effectiveness of cholesterol-lowering interventions, and how this information could be interpreted in a rational approach of cholesterol management in general practice.
Design- A systematic review of the literature.
Setting- No restriction on setting.
Materials- Papers reporting on the cost-effectiveness or cost-utility of prevention of (recurrent) coronary heart disease by reduction of hypercholesterolaemia in adults.
Main results- Thirty-eight studies, most cost-effectiveness analyses, were included. In 24 studies drug interventions only were analysed. Costs of screening in order to target cholesterol-lowering interventions to persons with hypercholesterolaemia were considered in 8 studies. Adjustments of the efficacy of the intervention for community effectiveness were rarely described. In three studies life years gained were adjusted for quality of life. Despite large variation in the outcomes, there is a constant tendency towards a less favourable cost-effectiveness ratio for intervening in persons without coronary heart disease compared to persons with coronary heart disease and for women compared to men.
Conclusions- The cost-effectiveness of cholesterol lowering interventions in the general practice setting seems to deteriorate when all relevant costs are taken into account and when efficacy is corrected for community effectiveness. Cholesterol-lowering intervention is more cost-effective in men compared to women and in patients with coronary heart disease compared to persons without coronary heart disease. Considerations from cost-effectiveness analyses should be incorporated into the development and implementation of national cholesterol guidelines for general practitioners. Standardisation of cost-effectiveness studies is important for future economic evaluations.

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Introduction

Controversy surrounds the benefit of cholesterol-lowering intervention to prevent coronary heart disease (CHD) in general practice patients. Internationally published guidelines on this topic differ in their restrictiveness of cholesterol screening, although they are based on the same type of evidence. The source of the controversy does not only seem to lie in the attitude of physicians towards preventive medicine, but also in the ambiguous clinical epidemiological evidence on effectiveness of cholesterol-lowering interventions. Personal norms and values probably play a major role in the interpretation and translation of evidence on effectiveness into policy[1]. A rational approach is needed towards cholesterol guidelines, in which attention is given to both effectiveness and cost-effectiveness of cholesterol-lowering interventions. Although physicians in general hesitate in integrating cost considerations in medical decision making[2], economic evaluation might provide an answer to the question of cost-effectiveness of cholesterol-lowering interventions.

The cost-effectiveness of cholesterol-lowering intervention depends firstly on its efficacy (can it work?), but finally on its community effectiveness (will it work when applied in the community?). Community effectiveness depends on the success of different steps, such as the physicians' ability to target high-risk individuals, the accuracy of screening, the extent to which uncertainties about the effectiveness of cholesterol lowering in untested patient groups are taken into account, or the patients' ability to maintain long-term compliance. Possible parameters that may be considered in an economic evaluation of a cholesterol-lowering intervention are listed in table 1[3-8]. The main body of cholesterol-lowering interventions in the general practice population, which is predominantly healthy and non-symptomatic, consists of screening and diagnostic actions rather than therapeutic strategies. It is therefore important to count the costs of screening, diagnosis, counseling and monitoring patients.

Cost and health implications of cholesterol lowering were already reviewed more or less systematically in four publications in which in total 10 economic evaluations were included[9-12]. Cost-effectiveness of cholesterol-lowering treatment ranged from <$0 to $1,800,000 per year of life saved. These reviews were incomplete and did not discuss the impact of the study methods used on the interpretation of the results for general practice policy.

Shortcomings of economic evaluations may have considerable impact on the relevance of the results[13] in the general practice setting. We are especially interested in the representativeness of the patient populations on which cost-assessments were based and the type of costs that were taken into account. Compliance towards cholesterol-lowering interventions is a problem, especially in the long term[14], and may decrease effectiveness. The discontinuation rates reported in randomised controlled trials of cholesterol-lowering drugs (about 30%[15 16]) are lower than the rates actually observed in the primary care setting[17]. Poor adherence is common when the treatment regimen is preventive rather than curative, when patients are asymptomatic for the target disease, and when the duration of the treatment

TABLE 1. MODEL FOR ECONOMIC EVALUATION OF CHOLESTEROL-RELATED INTERVENTIONS.

NET HEALTH CARE COSTS:

direct medical costs:
- the screening strategy: the selection of the part of the population that has to be screened as well as the frequency of screening
- the diagnostic strategy: the number of tests, the sequency of testing, further diagnostic testing following different results of the screening test, outpatient consultations or primary care consultations
- the therapeutic strategy:
  diet-therapy: education leaflets, guidance and monitoring by physician or dietitian
  drug-therapy: doses, frequency, number of medication days, guidance and monitoring by physician
- side effects of cholesterol-lowering therapy: costs of screening for and treatment of side-effects
- organisational costs: how and who, overhead costs, energy and maintenance, rent/housing

plus **direct non-medical costs:**
- transportation to and from medical services, care provided by family and friends

plus **indirect costs:**
- time spent by patient seeking medical services: change in productivity, time spent by family/friends

minus **savings in health care costs** due to prevention of disease
  direct benefits: health care resource savings
  indirect benefits: production gains from return to work

NET HEALTH EFFECTS:

several **possible endpoints** such as: change in serum cholesterol level or the expected number of life years gained, which are influenced by:
- screening and diagnostic accuracy
- efficacy of the intervention
- health provider compliance: refers to clinical process rather than clinical structure
- patient compliance
- coverage: describes whether or not the individual makes contact with the health professional

plus **adjustment for improvement/deterioration in the quality of life***
  Improvements in physical, psychological or social well being of patients or their carers, due to prevention of morbidity. Deteriorations in quality of life due to side effects of screening or treatment, loss of productive time (sick-leave, occupational disability), travel and waiting time, psychic disstress/inconveniences (e.g. anxiety through labeling, false-positives/false-negatives, eg. change of eating habits).

is long[18]. From the primary care perspective it is important to consider that intangible costs of undesired side-effects of cholesterol interventions might occur. It is the general practitioner, dealing with relatively healthy people and having a confidential and continuous relationship with them, who will be confronted with these kind of costs.

The objective of this systematic review is to evaluate published data on cost-effectiveness of cholesterol-lowering interventions, and to interpret the value of this information in the context of a rational approach of cholesterol-lowering intervention in general practice.

Methods

The studies in this review were english-language papers which had to fulfil three inclusion criteria: (i) the object of study was prevention of (recurrent) coronary heart disease by

targeting hypercholesterolaemia in adults; (ii) a full economic evaluation in the format of a cost-effectiveness, cost-utility, or cost-benefit analysis was carried out; (iii) data on the cost-effectiveness of the cholesterol-lowering intervention were presented separately from any other coronary heart disease related intervention.

Four search strategies were executed to locate relevant studies: (i) Medline 1966-1996, in which thesaurus and freetext key-words were combined; (ii) National Health Service Centre for Reviews and Dissemination Economic Evaluations Database, University of York (internet address: nhscrd.york.ac.uk); (iii) bibliography of health care cost-benefit and cost-effectiveness evaluations 1979-1990[19]; (iv) snowballing. The following key-words were used in Medline: *thesaurus;* hypercholesterolemia/economics, (hypercholesterolemia/all subheadings and cost-benefit-analysis/all subheadings), explode anticholesteremic-agents/economics; *freetext;* ((economic evaluation or cost-effectiveness analysis) and (cholesterol or hypercholesterole?mia) in title)).

A standardised form was used to extract data from the studies. Criteria for assessment of methods and parameters used in the economic evaluation[20-24] are listed in Table 2. Due to heterogeneity in the methods of measuring, the type of costs and outcomes, it was impossible to summarise the results by means of statistical pooling techniques.

TABLE 2. METHODOLOGICAL QUALITY OF THE ECONOMIC EVALUATIONS. CRITERIA FOR ASSESSMENT OF THE METHODOLOGICAL QUALITY AND THE NUMBER OF STUDIES THAT FULFILLED THE CRITERIA. TOTAL NUMBER OF STUDIES IS 36.

	Criteria for assessment of the methodological quality	no of studies
1	the (alternative) intervention(s) to be analysed to (who, what, where, why, when, and how) was/were precisely described	29
2	the perspective/viewpoint for the analysis was provided (society, insurers, health care system, hospitals, physicians, patients) was explicitely stated	9
3	the most reasonable alternative clinical interventions were being considered	22
4	the study sample, for which cost and outcome projections were made, could be judged on representativeness (experimental data, and/or observational data)	34
5	the types of costs that were used or considered in the analysis were explicitely defined	36
6	average and marginal costs were differentiated	11
7	quantities of resources were reported separately from the prices (unit costs) of those resources	28
8	an explicit description of the health effects (the primary outcome measure) of the intervention being studied was provided	35
9	health effects were based on community effectiveness data	5
10	if health effects have been valued details were given of the method used	0
11	a summary measurement of efficiency, such as a cost-effectiveness ratio, was calculated	38
12	an incremental analysis was reported, comparing the relevant alternatives	12
13	adjustments made for time (ie, inflation, are future costs and benefits discounted) were reported in detail (the discount rate should be given)	27
14	potential effects of important assumptions were measured in a sensitivity analysis by varying uncertain parameters and recomputing costs and effects	23
15	the conclusions reached were not sensitive to the assumptions and biases in the study	4

Results

Twenty papers were excluded from this review after careful consideration. In one study the cholesterol-related intervention was targeted at children instead of adults[25], two studies were cost-minimisation analyses[26 27], six studies were partial in stead of full economic evaluations, e.g. calculation of costs only[28-33], in seven studies the results on cholesterol-lowering interventions could not be separated from the combined interventions which were subject of study[34-40]. Two studies simulated a full cost-effectiveness analysis using hypothetical data only[41 42]. Double-publication occurred twice[43 44].

Thirty-eight studies fulfilled the inclusion-criteria. Most of these studies (n = 33) were published recently, in the nineties. Three of the studies were cost-utility analyses with Quality Adjusted Life Years in the denominator of the cost-effectiveness ratio. The other 34 included studies were cost-effectiveness analyses. The timespan of the evaluation ranged from four months to lifetime intervention.

The overall results on the methodological criteria are reported in Table 2. (Full tables with general and economic characteristics of the individual studies can be requested from the first author.) The perspective of the analysis was explicitely stated in nine studies, with a societal perspective in eight studies, and the patient's perspective in one. The most reasonable alternative interventions were being studied in 22 studies, whereas no alternative intervention at all was being considered in 13 studies. Data on effectiveness of the intervention were based on published RCTs in 31 studies. Observational data were also used in the calculations of effects in 23 studies, which was the Framingham Heart Study in 17 of these cases. Health effects were seldomly based on community effectiveness data; screening and diagnostic accuracy was accounted for in one study only. Adjustments of the effectiveness of the intervention for patient compliance was described in five studies. The discount rate was most often 5%.

In nearly two-third of the studies (n = 24) drug interventions only were considered for the analysis. Some relevant characteristics of these studies are outlined in table 3. In six studies the clinical outcome was expressed as the change in cholesterol level. In the other 18 studies the denominator of the CE ratio was Year Of Live Saved or averted myocardial infarction (twice). Drug therapy related costs were limited to the costs of the drugs in nine of these 24 studies. Non-medical costs or savings were calculated in two studies, namely unemployment savings. The study populations were limited to (middle-aged) men in nine studies, and were in most cases free of coronary heart disease. Most studies were based on the new-generation drugs, the statins. The goal of this review was to estimate the methodological quality of the published economic evaluations and their value for general practice policy, not to arrive at an average CE ratio. The CE ratios are reported in the table to show the wide variation in the CE ratios in and between studies, and general trends in cost-effectiveness. The comparibility of the CE ratios is low due to differences in many parameters, some of which are: differences in methodological quality, in populations studied (gender, age, presence of CHD, baseline cholesterol level), in types and intensities

TABLE 3. CHARACTERISTICS OF THE STUDIES WITH DRUG INTERVENTIONS ONLY. (YOLS = YEAR OF LIFE SAVED).

study	population (sex, age, chol, CHD)	intervention	alternative intervention	cost identification: direct medical costs/savings	other costs/ savings	CE ratio (price tariff date)
OUTCOME EXPRESSED IN CHANGE IN CHOLESTEROL LEVEL						
Schulman 1990[45]	?	various, applying RCT model	various, primary care model	drug costs monitoring costs screening side-e. treating side-e. savings in CHD care	-	$139-347 per 5 y % chol↓ (1989)
Lim 1992[46]	♂ + ♀ chol > 6.2	simvastatin	gemfibrozil	drug costs	-	$54-64 per month mmol/l↓ LDL (?)
Blum 1994[47]	?	lova, simva, prava, fluvastatin	-	drug costs	-	$15-52 per year % chol↓ (?)
Smart 1994[48]	?	simvastatin	pravastatin	drug costs monitoring costs	-	R6785-8674 patient reaching target level (1994)
Schrott 1995[49]	♂ + ♀ chol ?	colestipol lovastatin	placebo	drug costs	-	$21-28 per year % chol↓ (?)
Oster 1996[50] [51]	♂ + ♀ 20-70 chol ? 10% CHD	lovastatin	various, stepped-care	drug costs monitoring costs screening side-e.	-	$41-49 per year % chol↓ (1992)
OUTCOME EXPRESSED IN MORBIDITY/MORTALITY						
Himmel-stein 1984[52]	♂ 35-74 chol > 6.7 CHD -	cholestyramine	free care	drug costs savings in CHD care	-	$775600 per averted MI (?)
Weinstein 1985[53] [54]	♂ 45-50 chol > 6.7 CHD -	cholestyramine	-	drug costs savings in CHD care	-	$126000 YOLS (?)
Oster 1987[55]	♂ 35-74 chol > 6.7 CHD ?	drug therapy	-	drug costs monitoring costs treating side-e. savings in CHD care	-	$36000-1 m. YOLS (1985)
Kinosian 1988[56]	♂ chol > 6.9 CHD ?	cholestyramine	colestipol oat bran	drug costs monitoring costs savings in CHD care	unem-ployment savings	$17800-117400 YOLS (?)
Martens 1990[57] [58]	♂ + ♀ 35-74 chol > 7.5 CHD -	simvastatin	cholestyramine	drug costs monitoring costs savings in CHD care	-	♂: f46-100000 YOLS ♀: f128-162000 YOLS (?)
Sarma 1990[59]	♂ 40-57 chol > 5.2 CHD -	gemfibrozil	-	drug costs monitoring costs screening side-e. savings in CHD care	-	-$17800 per averted MI (?)

TABLE 3 CONTINUED.

study	population sex, age, chol, CHD)	intervention	alternative intervention	cost identification: direct medical costs/savings	other costs/ savings	CE ratio (price tariff date)
Hay 1991[60]	♂+♀ 35-55 chol ? CHD-	lovastatin	-	drug costs monitoring costs screening side-e. treating side-e. savings in CHD care	-	$9000-297000 YOLS (?)
Goldman 1991[61]	♂+♀ 35-84 chol ?	lovastatin 20 mg	lovastatin 40 mg	drug costs monitoring costs screening side-e. savings in CHD care	-	CHD-: $13000-330000 YOLS CHD+:$0-19000 (1989) YOLS
Glick 1992[62]	♂ 50 CHD - chol > 7.5	simvastatin	cholestyramine	drug costs savings in CHD care	-	£9600-36000 YOLS (1989)
Hjalte 1992[63]	♂ 37-64 chol > 6.2 CHD -	simvastatin cholestyramine	usual care	drug costs monitoring costs savings in CHD care	-	SEK149400-1,175m YOLS (1988)
Guibert 1993[64]	?	lovastatin gemfibrozil cholestyramine	-	drug costs monitoring costs savings in CHD care	-	Can$34687-0.4m YOLS (1991)
Goldman 1993[65]	♂+♀ 35-84 chol > 15.5 CHD -	lovastatin 20 mg	lovastatin 40/80 mg	drug costs monitoring costs savings in CHD care	-	$0-120000 YOLS (1989)
Martens 1994[66]	♂ 45 LDL ≥ 4.5 CHD -	fluva, lova, prava, simvastatin	no drug, fluvastatin 40 mg	drug costs monitoring costs savings in CHD care	-	Can$38800-56200 YOLS (1993)
Hamilton 1995[67]	♂+♀ 30-70 chol 10th perc CHD -	lovastatin for high risk p.	lovast. for low risk p.	drug costs monitoring costs screening side-e. savings in CHD care	-	♂: $20882-76749 YOLS ♀: $36627-155891 (1992/93) YOLS
Pharaoh 1996[68]	♂+♀ 45-64 chol > 5.5/6.6 CHD +/-	statin	-	drug costs savings in CHD care	-	CHD-: £420-1.4m YOLS CHD+: £6-143000 YOLS (?)
Ashraf 1996[69]	♂ chol ? CHD +	pravastatin	usual care	drug costs monitoring costs screening side-e. savings in CHD care	-	$7124-12655 YOLS (1995)
Jönsson 1996[70]	♂+♀ chol 5.5-8.0 CHD +	simvastatin	placebo	drug costs savings in CHD care	-	£5502 YOLS (1995)
Johannesson 1997[71]	♂+♀, 35-70 chol 5.5-8.0 CHD +	simvastatin	placebo	drug costs savings in CHD care	unemployment savings	♂: $<0-6200 YOLS ♀: <0-13300 YOLS (1995)

TABLE 4. CHARACTERISTICS OF THE STUDIES WITH INTERVENTIONS WHICH WERE NOT LIMITED TO DRUG INTERVENTIONS. (YOLS = YEAR OF LIFE SAVED, QALY = QUALITY ADJUSTED LIFE YEAR).

study	population (sex, age, chol, CHD)	intervention	alternative intervention	cost identification: direct medical costs/savings	other costs/ savings	CE ratio (price tariff date)
OUTCOME EXPRESSED IN CHANGE IN CHOLESTEROL LEVEL						
Oster 1986[72]	♂ chol > 6.7	cholesterol lowering	-	savings in CHD care	unemployment savings	$1-16000 15% chol↓ (1980)
Wilson 1992[73]	factory employees	screening + diet therapy (+ incentive)	screening	screening costs diet therapy costs administration costs	-	$2-5 % chol↓ (1989)
Tomson 1995[74]	♂ + ♀ 25-54 chol 7.0-7.8 CHD -	intense diet therapy	diet therapy	diet therapy costs monitoring costs	loss of working time, transport c.	SEK 229-974 % chol↓ (1993)
McGehee 1995[75]	♂ + ♀ 20-80 chol ?	diet therapy	-	diet therapy costs	-	$19 % chol↓ (?)
OUTCOME EXPRESSED IN MORBIDITY/MORTALITY						
Kelley 1990[76]	♂ 40 chol > 6.9 CHD ?	diet therapy, various drugs	-	diet therapy costs drug costs treating side-e. savings in CHD care	unemployment savings	-$2536-108826 YOLS (1987)
Reckless 1990[77]	♂ + ♀ 20-65 chol ? CHD ?	screening + diet therapy (+ drug ther.)	-	screening costs diet therapy costs drug costs monitoring costs savings in CHD care	-	£550 QALY (1989)
Med Adv C. '90[78]	♂ + ♀ 25-69 chol ? CHD ?	screening + diet therapy (+ drug ther.)	-	screening costs diet therapy costs drug costs monitoring costs savings in CHD care	-	£2852 QALY (?)
Assmann 1990[79]	♂ + ♀ ? chol ? CHD -	West Germany guidelines	-	diet therapy costs drug costs monitoring costs savings in CHD care	-	♂: DM30-40000 YOLS ♀: DM86-110000 YOLS (?)
Kristiansen 1991[80]	♂ 40-49 chol ? CHD ?	health promotion, diet (+ drugs)	no care	health prom. costs screening costs drug costs monitoring costs screening side-e. savings in CHD care	-	health pr: £10 QALY diet: £100546 QALY diet + dr: £125860 QALY (1990)
Weissfeld 1992[81] [82]	♂ 50-60 chol ? CHD ?	NCEP guidelines	no care	screening costs diet therapy costs drug costs monitoring costs screening side-e. savings in CHD care	-	$12761-22553 YOLS (1989)

TABLE 4. CONTINUED.

study	population (sex, age, chol, CHD)	intervention	alternative intervention	cost identification: direct medical costs/savings	other costs/ savings	CE ratio (price tariff date)
Kinlay 1994[83]	♂, 35-64 chol ? CHD ?	screening + diet therapy (+ drug ther.)	-	screening costs diet therapy costs drug costs monitoring costs savings in CHD care (>80% of the costs were for drug therapy)	-	$A335825-1.5m averted CHD event (1988/89)
Field 1995[84]	♂ + ♀ 35-64 chol ? CHD ?	screening high risk patients	screening all patients	screening costs counseling costs costs of therapy monitoring costs savings in CHD care	-	♂: £2720 YOLS ♀: £5040 YOLS (?)
Johan-nesson 1996[85]	♂ 30-59 chol ? CHD -	usual advice + drugs intensive adv. (+ drugs)	usual advice	counseling costs costs of diet therapy drug costs monitoring costs savings in CHD care	loss of working time, transport c.	$61000-223000 YOLS (1991)
Plans 1997[86]	♂ + ♀ 35-69 chol 5.7-9.8 CHD ?	high risk diet therapy	population diet approach	screening costs diet therapy costs monitoring costs savings in CHD care	-	♂: $6270-61439 YOLS ♀: $28067-171459 YOLS (1990)

of intervention, in the assessment of the net health effect of the intervention which depends on the quality of the underlying evaluation studies, in the extend of costs measured, in the differences in cost calculations between health care systems/countries, in the degree of subjecting assumptions used to sensitivity analyses, or in the differences in monetary units and price tariff dates at the time of calculating the CE ratios. Nevertheless, there seems to be a consistent tendency towards a less favourable cost-effectiveness ratio for women compared to men and for persons without coronary heart disease compared to persons with coronary heart disease.

The 14 studies in which interventions were not limited to drug interventions are described in table 4. Because most of these studies report about non-referred patients, this group of studies seems more representative for the general practice setting than the group of studies described in table 3. In the study of Oster published in 1986 calculations were made with Framingham data for people with different levels of serum cholesterol to assess the cost-effectiveness of cholesterol lowering by whatever kind of intervention. Nearly all (n = 12) studies considered diet therapy in the calculations. Costs of screening in order to target the cholesterol-lowering interventions to persons with hypercholesterolaemia were considered in 8 studies. All three cost-utility analyses fell in this group of studies. Again, despite high variation, the same tendencies are seen in the CE ratios.

Discussion

Most economic evaluations of cholesterol-lowering interventions focus on certain drugs, with cost calculations limited to direct drug-related costs. Little is known about cost-effectiveness of cholesterol-lowering interventions including screening and diagnostic costs of targeting the persons with hypercholesterolaemia, which is an important part of risk management in general practice. Patient compliance, indirect non-medical costs and intangible costs were hardly or not taken into account in the economic evaluations. Both the variation in parameters that were used in the economic models as well as the variation in methodological quality in the studies is striking. Cost-effectiveness of cholesterol-lowering drug therapy in patients without CHD was highly variable depending on age and risk and generally unfavourable. The cost-effectiveness of screening and therapy of hypercholesterolaemia in persons free of coronary heart disease seems less favourable if indirect patient-related costs are taken into account. Despite the large variation in the cost-effectiveness ratios in and between the studies, there is a consistent tendency towards a less favourable cost-effectiveness ratio for women compared to men and for persons without coronary heart disease compared to persons with coronary heart disease.

Some assumptions used in many of these studies need attention. It was often assumed that lowering a person's cholesterol level would change his or her risk profile in the direction of the risk of a person whose cholesterol level had never been elevated. It was also assumed that there will be no side-effects from cholesterol reduction, and that there will be no changes in the rates of noncoronary morbidity in persons whose cholesterol levels are reduced[1]. Another assumption was that overall mortality decreases, which was only recently confirmed in two statin trials[17 87]. Pharoah's, Jönsson's and Johannesson's analyses deserve special attention as they were based on data from these trials. Cost effectiveness ratios were in general unfavourable for the subgroup of persons without coronary heart disease, despite the fact that only drug costs were considered. Another assumption applicated in most studies is the correct classification of individuals with respect to the serum cholesterol level. Measurement error in the determination of lipid levels alters the effectiveness of cholesterol interventions[88 89], it worsens the cost-effectiveness ratios of case finding and treatment programs by 11-12%[90] or even by 17 to 29%[91].

There are specific limitations of the economic evaluations from the viewpoint of the primary care field. Costs of targeting persons with hypercholesterolaemia were not calculated in 29 out of the 36 studies. This is reasonable in the two studies restricted to patients with pre-existing coronary heart disease, since the cholesterol-lowering therapy will simply be added to standard treatment and will incur few additional costs associated with doctor time. But, in asymptomatic people, there would be additional costs associated with cholesterol testing in a healthy population, and increased use of doctor time in those subsequently treated. A restrictive screening policy already increases workload considerably[92 93 94], which can lead to considerable costs[28 30 32].

Another limitation is that intangible costs were hardly discussed in the studies. Even small disutilities associated with screening and treatment seem to be able to outweigh the benefits of aggressive cholesterol-lowering strategies[95]. Diet therapy e.g. seemed cost-effective per YOLS but far less favourable per QALY. Although it is not always confirmed[96 97], patients may exhibit adverse psychological response to being labeled with the diagnosis of hypercholesterolaemia. Failure to acknowledge some of the specific complexities of hypercholesterolaemia (eg. natural fluctuations in serum cholesterol levels, variability of response to diet) may result in considerable anxiety[98]. Healthy (asymptomatic) persons diagnosed as hypertensive patients are at increased risk of work absenteeism and other behavioural changes[99 100]. An increase in work absenteeism could not be found in persons that were positively screened for hypercholesterolaemia[101], but, higher scores on anxiety and lower scores on mood were reported, three months to a year after cholesterol screening[102-105]. Especially the elderly seem at risk for labeling effects because they have a somewhat higher serum cholesterol[106].

The reverse of labeling is the feeling of invulnerability after detection of a normal serum cholesterol level (a certificate of health) or the start of cholesterol-lowering drug therapy (the magic bullets). It may encourage unhealthy behaviour in people at high risk[107]. Normo-cholesterolaemic persons may not improve their lifestyle as much[107 108], or might even deteriorate their lifestyle[109] compared to positively screened persons. False-negative results may produce the false sense of security, resulting in delays in seeking medical care when warning symptoms become present[110]. Screening programmes affect a large number of people relative to the number who benefit. A small adverse affect of screening on quality of life, health promoting behaviour, or individuals' capacity to care for themselves could have an impact on the public health which outweighs any health gain to be achieved by screening[111].

Thus, the efficiency of cholesterol lowering interventions might be reduced when some of the assumptions used in the economic evaluations are critically evaluated, when screening and diagnostic costs are calculated for cholesterol-lowering interventions in persons without CHD, when adjustments are made for patient compliance and when intangible costs are considered. Incorporation of the disutility of screening and treatment may result in less interventionist and less costly policies. On the other hand, costs of screening (targeting symptomless persons with hypercholesterolaemia) can be much lower if guidelines are simplified[29] and accuracy of classification is improved[112].

We conclude that the methodological quality of the published economic evaluations is disappointing in several aspects, with specific limitations from the viewpoint of the primary care field. Cholesterol-lowering intervention is more cost-effective in patients with CHD than in persons not known with CHD and in men compared to women. Considerations from cost-effectiveness analyses should be incorporated into the development and implementation of future national cholesterol guidelines. The need for standardisation of this kind of studies is obvious[113]. Recently published guidelines for standardisation should have impact on future economic evaluation studies[8 24 114], in order to build decisions

about practice guidelines on a balance of rationality on the one hand and individual norms and values on the other.

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Chapter 9

Discussion

In this chapter we will summarise the main results and relate the conclusions of the earlier chapters on the basis of the topics 'investigation of usual care', feasibility of the guidelines' and the 'evidence base of the guidelines'. This step is visualised in the research model in chapter 1 (page 8). Some methodological considerations that have not yet received attention in the chapters will be taken into account before we go into the interpretation and discussion of the results. Finally, we will highlight recommendations for updating the guidelines, for strategies for implementation, and for further research in this field.

Summary of the main results

Investigation of usual care

Specific problems with current general practice concerning diagnosis and therapy of hypercholesterolaemia in relation to the cholesterol guidelines were found. Managing hypercholesterolaemia proved not to be a clear-cut task for Dutch GPs in the years before the guidelines were published. In the years since the DCGP standard on Cholesterol was published, when GPs are supposed to be familiar with the guidelines, adherence to it has been low. It can be concluded from chapter 2 to 4 that inter-doctor variation in cholesterol management by Dutch GPs is considerable and persistant, despite a rising trend in cholesterol testing. The main problems are the adherence to age criteria for screening (about one-fifth of the patients tested for the first time are older than 65 years), the adherence to indications for screening related to the patient's risk profile (less than one-third of the patients with an indication for testing were actually tested), the repetition of testing necessary to diagnose hypercholesterolaemia (repeated measurements to diagnose hypercholesterolaemia was performed in less than 0.5% of the cases), and the doctor's and patient's compliance to diet therapy.

Feasibility of the guidelines

It was concluded from chapters 5 and 6 that adherence to the guidelines did not improve, despite a solid intervention. The development of the implementation strategy was optimised by assessment of the possible barriers and needs perceived by GPs to working according to the guidelines. Although the quantity of cholesterol testing increased significantly in the course of the trial, which could probably be explained by the parallel rise in desktop test-ordering devices in the practices, the quality of cholesterol testing did not. It even deteriorated in some respects. The programme for improvement failed to have relevant impact on either knowledge and attitude or actual performance in the follow-up of the implementation trial. Many barriers to change, both related and not related to the professional, were assessed. Profession-related barriers in the area of knowledge or attitude were a lack of priority for prevention ("I just don't think of case finding"), the time-consuming nature of preventive procedures (without reimbursement), the trouble both for the GP and the patient of repeating the cholesterol test three times, hesitation to intervene in a patient's lifestyle, and doubt about the cost-effectiveness of cholesterol intervention. Profession-related barriers in the area of skills were difficulties to change practice routines, and feelings of incompetence in guiding patients for diet therapy. Other barriers were not directly related to the professional: the complexity of the guideline algorithm, practical problems in monitoring the risk profile, difficulties to change both practice routines and lifestyle for the patient ("diet therapy is frustrating, both for the patient and the GP"), patients actively demanding for cholesterol testing ("I'm a doctor, not a negotiator"), interference by cardiologists'/internists' cholesterol management which deviates from the general practice guidelines, and lack of cooperation with these specialists.

Evidence base of the guidelines

The main conclusion from the evidence reviewed in chapter 7 was that no effect of cholesterol lowering on total mortality was seen despite a decrease in non-fatal myocardial infarction. No conclusions could be drawn for women, older and younger men, and morbidity in general. Being symptomatic for CHD rather than being hypercholesterolaemic seemed to be an important predictor for the benefit of cholesterol lowering.

From the review of the newly available evidence (supplement to chapter 7), it was concluded that the effect of cholesterol lowering is now established in patients with CHD. The recent finding that cholesterol lowering reduced total mortality in CHD patients is of great importance in this matter. The evidence is convincing for the subgroup of middle-aged white men. Again, there is far less information and more uncertainty on women and older and younger men, and the interpretation of the smaller benefits of cholesterol lowering in persons without CHD. Screening on serum cholesterol levels is most likely to be useful when done in populations at high short-term risk of dying of CHD, such as survivors of myocardial infarction and middle-aged men with multiple cardiac risk factors.

Cost-effectiveness of cholesterol-lowering interventions in the general practice setting is likely to deteriorate when efficacy ("can it work?") is corrected for community effectiveness ("does it work in daily practice?"), and when all relevant costs are taken into account. The main thrust of cholesterol-lowering interventions in the general practice population, which is predominantly healthy and non-symptomatic, consists of screening and diagnostic actions rather than therapeutic strategies. It is therefore important to count the costs of screening, diagnosis, counselling and monitoring patients. There is a lack of high quality information on cost-effectiveness of cholesterol lowering in general practice in this respect. From the viewpoint of cost-effectiveness it is less favourable to intervene in persons without CHD compared to persons with CHD and in women compared to men.

Methodological considerations

The research model

The evaluation of the feasibility of the guidelines on the one hand and the evaluation of the evidence base for the guidelines on the other are situated as parallel projects in the research model, as was outlined in chapter 1. Nowadays, checklists are being published to appraise critically the quality of practice guidelines[1 2 3 4]. These checklists focus on the evidence base or scientific validity of the guidelines. But guidelines are usually developed on areas in medicine which are characterised by complex interventions or by controversy. Controversy due to a lack of evidence, to contradictory evidence, or to different interpretations of the evidence. These kind of guidelines need continuous updating. We still feel, as was argued in chapter 1, that updating should be accompanied by evaluation of the feasibility of the guidelines in daily practice. Apparently, in the light of the results presented in chapters 5 and 6, general practitioners' adherence to cholesterol guidelines is not a logical consequence of the dissemination of the guidelines. What is needed is either

specific implementation strategies to improve adherence to the guidelines, or changing the content of the guidelines to ensure that GPs concentrate on the crux of the guidelines, thereby demonstrating good adherence to at least the key-part of the guidelines.

One aspect of the scientific evidence of the cholesterol guidelines was not evaluated in this thesis, namely the diagnostic accuracy of cholesterol testing. As was outlined in chapter 1 community effectiveness is defined as "efficacy x diagnostic accuracy x health provider compliance x patient compliance x coverage". The question of the diagnostic accuracy can be directed at two phenomena: the predictive value of the total serum cholesterol and the performance of test devices or test protocols. The predictive value of total serum cholesterol in relation to CHD is still under discussion. Although the diet-heart hypothesis was not rejected in the various RCTs of cholesterol lowering, the strength of the relation between cholesterol and CHD was heterogeneous and weaker than expected. Combinations with other predictors, such as the ratio of serum total cholesterol concentration to high density lipoprotein cholesterol, are claimed to be better than total serum cholesterol concentration alone[5]. Etiological research to disentangle the complex relation between risk factors and CHD is continuing to elucidate the mechanism of atherosclerosis further. The complex relationships between diet, serum cholesterol, atherosclerosis and mortality and their interactions with genetic and environmental factors suggest that the effects of simple dietary prescriptions are unlikely to be predictable[6]. Numerous determinants of CHD are mentioned in etiological research; oxidised LDL, a family history of CHD, apolipoproteins, homocysteine, fetal undernutrition, haemostatic factors like fibrinogen or factor VIII concentration, high serum albumin, iron overload, selenium, IgE, C reactive protein, or even past infection with cytomegalovirus or chlamydia. There is a need for a valuable diagnostic tool, which should have a higher predictive value for the occurrence of CHD than total serum cholesterol. At present there is no reliable noninvasive screening technique available to directly measure the risk of coronary artery occlusion.

Investigation of usual care

There are a variety of methods to investigate usual care. GPs can be questioned about their performance in daily practice on cholesterol screening and management. This may result in non-valid data because what is actually measured are concepts like knowledge, or socially desirable performance. A superior method to investigate the usual care of GPs in this field would of course be direct observation of actual performance during their practice work. Clearly, these kinds of observations require lots of time, money and personnel, and thus were not realistic in this research project. Therefore we chose to investigate the usual care through indirect assessments of the actual performance, like consultation registrations or chart audits. By applying different independent methods and by making use of existing databases we tried to create a valid and complete picture of the usual care in general practice. The results of the analyses of the three data sources (chapters 2-4) seem valid because they point in the same direction with comparable results on the quality of care. Analysing the longitudinal data of the Coordinating Diagnostic Centre of Maastricht

allowed changes in quantity or quality of cholesterol screening to be measured (chapter 4). The only aspect of care that could not be assessed reliably was the cholesterol-lowering drug prescribing by GPs.

Feasibility of the guidelines

The investigation of the usual care provided a better understanding of the problematic areas of the guidelines. These were confirmed in questionnaires and discussions with GPs, in which they were encouraged to give a critical opinion on both the content and the feasibility of the cholesterol guidelines. The programme for improvement was based on these barriers and needs perceived by GPs, as is described in appendix 2. The programme was on the one hand multi-faceted, that is composed of several different strategies developed to influence the GPs' behaviour, but on the other hand it was an unidimensional programme because it was aimed at the professional, and not at external influences of the GPs' behaviour.

To test the feasibility of the guidelines a pretest-posttest design is indicated, to measure whether GPs change their behaviour in the direction of the guidelines. The participating GPs were randomly divided in two groups in order to measure the effect of the programme for improvement on the GPs' behaviour. Our null-hypothesis was that the GPs did need this programme, considering the many barriers and needs that were assessed, and that it would help them in adhering to the guidelines. The trial was deliberatedly not designed with one control group and several intervention groups varying in intensity of the programme for improvement. This was because the central theme was the feasibility of the cholesterol guidelines and not the effectiveness of the different components of the programme for improvement.

Could the negative results be caused by methodological flaws? The sample size, 20 general practices with 32 GPs, was not very large. The results of the trial may have gained in precision if more GPs would have participated in the trial. However, it is highly unlikely that the direction of the results would have changed considering both the decrease in quality of performance instead of an improvement and the confirmative results with multi level analysis. The impossibility to blind the control group may have caused a change in the desired direction, because measuring behaviour may have had an intervening effect (the Hawthorne effect). We tried to maximise the contrast between the groups by not letting the control group GPs register cholesterol contacts during baseline, thereby including the baseline consultation registration in the intervention procedure.

The 32 GPs that took part in this study are in many respects - e.g. gender and list size - representative for Dutch GPs, but they are a little younger and more likely to be working in group practices. They are also liable to selection bias because of self-selection of the more motivated GPs for this subject during the recruitment period. These characteristics, being younger, working in group practices, and being more motivated, are reported to be factors associated with likelihood of adopting practice guidelines. Thus the implementation study probably overestimates the appropriateness of the GPs' performance in relation to

the guidelines. This means that a broader implementation of the guidelines in general practice would have revealed even less adherence. Nevertheless, this study provides good insight into barriers that limit adherence to the national guidelines. Barriers that inhibit motivated GPs will play an even larger role in other GPs[7].

Evidence base of the guidelines

Much attention was given in the meta-analysis of randomised controlled trials of cholesterol lowering to a judgement of the quality of the trials included (chapter 7). Three independent experts in the field of CHD and/or methodology of clinical trials independently assessed the quality in a standardised way. The studies were presented in a blinded format to the judges; they were blinded for the journal in which the trial was published, for the name of the trial and the investigators, for the results of the trial, as well as for geographical and time indications. The necessity of such a blinded assessment was recently affirmed. Blind assessment of reports produced significantly lower and more consistent scores than open assessments[8]. A major disadvantage of judging the quality of the studies is that it is dependent on the information available in the reports. This disadvantage can only be avoided if journals adopt more uniform requirements for trial reporting[9]. Application of the random effects method, which is advocated in case of heterogeneity of the pooled result, would not have affected the point estimate, but would have produced wider confidence intervals for the pooled estimate than fixed effects methods.

The publication of twenty other meta-analyses at the time the meta-analysis reported in chapter 7 was finished raises the question how many other meta-analysis were left unpublished. Considering the huge efforts needed to perform meta-analysis in a standardised and reproducible way with blinded quality assessment, there is a great need for a coordination and collaboration in reviewing evidence. The Cochrane Collaboration is an example in this respect, where subjects which are under review are registered[10].

Data extraction and quality assessment in the review of economic evaluations was executed by one of the investigators only (chapter 8). This can be justified by the explorative instead of affirmative character of this review. The objective was not to arrive at an average cost-effectiveness ratio, the main goal was to appraise the methods used in the evaluations. Summarising the results of the economic evaluations was of secondary importance.

The high level of heterogeneity of the methods used in the economic evaluations and the often oversimplified cost calculations hamper rational interpretation of the results. Different expressions of the results in the cost-effectiveness ratio, like average and incremental cost-effectiveness ratios, even obscured clear interpretation. The difference between these two types of ratios is that the incremental cost-utility ratio reveals the cost per unit of benefit of switching from one treatment strategy (usually current practice) to a new strategy, whereas average cost-effectiveness reflects the cost per benefit of the new strategy independent of alternative strategies[11]. Standardisation of these kinds of studies

must have high priority in future economic evaluations.

Alternative approaches to measure efficacy are the "number needed to treat to prevent one adverse event"[12] and the assessment of benefit and harm of treatment separately for individual patients[13]. The number needed to treat can be expressed as the reciprocal of the absolute risk reduction: the number of patients with a given disorder that a physician must treat in order to protect one of them from the disorder's potential consequences. It can also be used as a measure to individualise treatment[14]. Recently a method for grading health care recommendations was proposed in which scientific validity and cost-effectiveness considerations are combined[1]. A threshold number needed to treat at which benefit exceeds the risks of therapy is calculated with parameters such as costs of treating the number of patients that need to be treated to prevent one target event, the cost of treating one target event, and the dollar value we assign to preventing one target event.

Discussion of the main results

Investigation of usual care

The discrepancy between current cholesterol test ordering behaviour and the guidelines does not necessarily mean low quality of care. Medical practice remains fundamentally an interpersonal experience, drawing on the rich interaction between practitioner and patient[15]. Nevertheless, it seems that efforts should be directed at increasing cholesterol testing in those with positive CHD profiles because the failure to test those likely to benefit came out as a major problem. Doing this would increase the workload of GPs; in fact at least one in every eight adults, having a positive risk profile for CHD and being in the 18-65 years age group, has to be tested when this guideline is followed. Considering the high proportion of patients with elevated serum cholesterol[16], the burden on the GP goes beyond testing because for all those whose cholesterol is raised repeated tests will be needed, and some will require monitored dietary advice (and drug therapy).

It is remarkable that, while the evidence for the benefit for cholesterol lowering is poorer for women than for men, relatively more women than men of 65 and older are tested. The low and even deteriorating performance on the diagnosis of hypercholesterolaemia, the stepwise repeat testing of serum cholesterol, is alarming. Insufficient repeat testing will impair the precision of diagnoses and the cost-effectiveness of cholesterol testing[17].

The quantity of cholesterol testing increased over the years 1984-1992 (chapter 4), and also during the course of the feasibility study in the 20 practices (1992/93). What are the implications of the rising trend in test ordering on health care costs? Increased testing takes a lot of time and medical resources; on the basis of charges for reimbursement, the costs of cholesterol testing at the DCC Maastricht increased from $8,557 in 1986 to $16,986 in 1992. For all Dutch GPs this would imply an increase in costs of about $700,000 over the same period. This implies far higher costs considering the number of patients that need management of hypercholesterolaemia. The high proportion of patients

with elevated serum cholesterol (≥ 6.5 mmol/l) (45% in 1992) implies that 150,000-160,000 Dutch patients per year might be considered for treatment. This already results in $2.5 million on consultation costs, not to mention potential costs of diet and drug therapy. The increasing availability of a desktop testing device for cholesterol testing may further contribute to a rise in cholesterol testing[18], which may be as high as 50%[19] or even 100%[20].

The only aspect of care that was not described, due to lack of data in this project, is the cholesterol-lowering drug prescribing by GPs, especially the trend in the new-generation drug prescribing. Cholesterol-lowering drug prescribing has increased considerably in several countries during the last ten years: three to sixfold in a period of 10 years or less[21-24]. In 1991 the overall prevalence of use of lipid-lowering drugs in a French professional population was 7.7%[25]. Low adherence to indications for HMG-coA reductase inhibitor prescriptions was reported[26 27], and improvement seems needed[28]. GPs' level of insight into prescribing policies of lipid-lowering agents proved to be low[29].

Feasibility of the guidelines

Why did the implementation of the guidelines with such an intensive programme for improvement not show an effect on performance? According to the literature, the programme for improvement ought to be a solid behaviour changing intervention[30].

One reason for the lack of success might be the top-down character of the implementation procedure. It might be a prerequisite for successful implementation of practice guidelines that the GPs themselves can adapt the guidelines to local needs[31]. Local ownership of guidelines may be important. Perhaps it makes more sense to produce evidence reports on a national level instead of practice guidelines on a national level. Evidence reports, such as the Cochrane Collaboration reviews, could be interpreted locally in terms of practice recommendations. Thus, different practitioners can interpret them differently depending on such criteria as the characteristics of their patient population, personal norms and values, or considerations of feasibility. Alternatively, practice guidelines should routinely include accessible presentation of treatment outcomes on benefit (e.g. quality adjusted years of life gained), hazard (e.g. number needed to treat), and costs for a range of absolute risks[32]. These measures enable patients and their doctors to weigh the pros and cons of intervention in their particular circumstances. Considering the large number of barriers to change, it is likely that the cholesterol guidelines would have been less complex after adaptation in a local consensus procedure.

Several other reasons for the lack of effect of implementing the guidelines might have played a role, like the preventive character of the cholesterol topic. Doctors are educated and prepared for investigating symptomatic patients and caring and curing the sick, rather than for keeping the healthy ones healthy. A systematic and supportive public health approach to professional, patient and organisation-related barriers to the delivery of preventive services is needed[33-35]. Especially in preventive care it seems important to ensure that efforts to change doctors' clinical behaviour meet with prevailing reimburse-

ment and administrative policies[36]. Other reasons for the lack of effect might be found in external influences on the GPs' behaviour, such as demanding patients or marketing activities of drug companies who provide desktop test devices. These external influences might have played a major role in the cholesterol screening activities of the GPs during the trial, maybe more decisive on feasibility of the guidelines than the intervention. Recently, the hypothesis was tested that nonclinical patient characteristics influence cholesterol management. The payment source, patients with private insurance were tested more often, was found to explain part of the variation between physicians[37].

During the investigation of current care and during the execution of the trial the proportions of demanding patients, the patients who actively requested for cholesterol testing, were consistently high; 20% of the patients tested at the Maastricht Diagnostic Coordinating Centre in 1992, 22% of the patients tested during the intervention period of the trial, about 40% of the patients tested during the follow-up of the trial. It might be important therefore to investigate patients' experiences or preferences regarding cholesterol screening and management. Insight into patients' preferences might influence opinion on feasibility and therefore the content of the guidelines. It might even be appropriate to make guidelines flexible with regard to patient preferences[38] [39]. Therefore, it was decided during the project to have a small inquiry as a pilot study at the end of the trial among patients that were confronted with the cholesterol guidelines (Table 1). The results of this survey suggest that patients appreciate the case finding situation, that they are willing to cooperate with repeat testing, that a considerable proportion of the patients actively ask for cholesterol testing, and that they are upset if their GP does not reward a request for testing ("What harm can be done with a cholesterol test?"). It must be difficult for GPs to negotiate with the patient when a request for testing does not match with the indication for testing.

Evidence base of the guidelines

A critical look upon the scientific base of the guidelines shows that the ongoing debate about which high-risk group benefits most from cholesterol screening needs clarification. The scientific validity of the guidelines has not gone unquestioned and cholesterol guidelines have been contradictory over the years. Some doctors believe the controversy about the effects of lowering cholesterol to be one of the most damaging false-negative results in the whole history of medical statistics, while others think that lowering cholesterol does little or nothing to reduce mortality. Variability between doctors in interpreting the evidence will reflect the different opinions of doctors on risk or the value they ascribe to a given health status. The seed of the controversy often lie in the personal norms and values which play a role in the interpretation of the evidence. It is often possible to find scientific justification for policies that best fits an individual's preconceptions. The variation in selection of trials in the numerous published meta-analyses is perhaps symbolic. Ravnskov explored the magnitude of quotation bias in some important reviews. About half of the RCTs on cholesterol lowering with negative findings were ignored, the

TABLE 1. SUMMARY OF THE PATIENT SURVEY. METHODS AND MAIN RESULTS.

Patients' experiences with the guidelines were investigated through a structured telephone survey. The GPs participating in the trial were asked to provide the investigator with informed consent of ten patients of whom they had registered at least one cholesterol consultation during the follow-up measurement. Most questions were constructed with answer-categories (seven-point scale) with the following extremes: self-evident/ surprising, positive/ negative, reassuring/ frightening. In case a patient was not confronted with a certain aspect of the cholesterol guidelines, his or her opinion was asked for the imaginary situation, e.g. "imagine that you would like to have your cholesterol tested, but your GP refuses to fulfil your request because he/she thinks it is not necessary.....". The results were analysed for internal consistency with Cronbach's alpha to select coherent sets of questions, and explored with descriptive statistics.

After informed consent was given, 125 patients (64 from 11 GPs in the intervention group and 61 patients from 12 GPs in the control group) were interviewed by phone. Of these 125 patients 116 had had their serum cholesterol tested in the previous year, which was initiated by 46% of these patients. None of the patients to whom a cholesterol test was offered unexpectedly (case finding) found that their attention was distracted of the reason for encounter. A cholesterol-lowering diet had been prescribed to two-thirds of the 125 patients sometime in the past. Fifteen percent of these patients were supported by their GP, 1% by the practice nurse, 29% were referred to a dietician, and 55% of these patients were given diet advice without any support. Nine percent of the 125 patients had actively requested for cholesterol-lowering drugs in the past.

Three sets of questions about patient experiences were selected after reliability analysis, with a Cronbach's alpha of at least .70. Patients feel positive and reassured when the GP offers a cholesterol test totally independent of the reason for encounter; they judge it as self-evident. Patients feel also positive, reassured and not surprised if the GP repeats blood testing once or twice in 2 months' time. Patients are surprised, negative and a bit frightened if the GP dissuades them or refuses an active request for cholesterol testing.

PATIENTS' EXPERIENCES ON SEVERAL SITUATIONS, REAL OR IMAGINARY. MEAN SCORES ON SEVEN-POINT SCALES* (SD).

	self-evident/ surprising	positive/ negative	reassuring/ frightening
the GP offers a test totally independent of the reason for encounter (n=38, α=.87)	2.7 (1.6)	2.2 (1.3)	2.6 (1.6)
cholesterol blood testing is repeated once or twice in 2 months' time (n=53, α=.70)	1.8 (1.0)	1.9 (0.9)	2.3 (1.3)
dissuasion or refusal of cholesterol testing after the patient requests it (n=125, α=.80)	5.9 (1.3)	5.7 (1.4)	4.9 (1.5)

* 7-point scale, eg: 1= very self-evident, 2= self-evident, 3= a bit self-evident, 4= no opinion, I don't mind, 5= a bit surprising, 6= surprising, 7 very surprising

About half of the RCTs on cholesterol lowering with negative findings were ignored, the rest were quoted irrelevantly, or insignificant findings in favour of the hypothesis were inflated[40]. Some believe that the controversy on cholesterol guidelines is influenced more by political and economic factors than by evidence of health benefit[41]. The method of developing the guidelines determines to a large extent the scientific validity of the guidelines[2 42]. A higher level of evidence might be needed, accompanied by descriptions of the strength of the evidence, as well as information on cost-effectiveness of screening for patients with hypercholesterolaemia in the primary health care setting, to convince GPs of the importance of certain guidelines[43].

From the update of the new evidence available it was concluded that the effect of cholesterol lowering is established in patients with CHD. The findings of the Scandinavian Simvastatin Survival Study (4S) justify treatment of survivors of myocardial infarction,

transferability of the results to real-life patients remains the critical, unanswered question, because there is far less information on women and older and younger men. Whether these new findings can be extrapolated to persons without CHD is an even more difficult question, because it is uncertain how the smaller benefits of cholesterol lowering in persons without CHD should be interpreted. Cholesterol-lowering interventions might probably be extended to persons without CHD provided that it is targeted strictly at patients with a risk of CHD similar to or higher than that of patients in the 4S study. What, then, is exactly the cutoff point in the level of CHD risk that makes it worthwhile to intervene on the cholesterol level? The threshold number needed to treat[13] and the Sheffield risk tables[44-46] try to answer this question.

The authors of the Sheffield risk tables recognise the fact that the cholesterol concentration confers a specified risk of CHD which varies among individuals. There is growing consensus that treatment of cardiovascular risks should be based on multiple rather than single factors. The tables are based on multifactorial risk calculations and are simplified in several respects, such as dichotomising hypertension in present/not present, or the exclusion of high density lipoproteins as a risk factor. The tables can be used as a guide to decisions on screening and/or treatment, according to the policy that individual doctors choose to adopt, and the personal wishes of the individual. It will require, though, that doctors and the public think in terms of measuring coronary risk rather than measuring cholesterol. The Sheffield group considers treatment appropriate at a specified level of CHD risk, namely the patient's risk of a coronary death is 1.5% a year or of an event rate of 3.0% per year. Advice to stop smoking, exercise, and improve diet remains the mainstay of intervention.

The threshold number needed to treat as proposed by Gyatt and others[13] is calculated on information both on efficacy as well as cost-effectiveness. Some people are concerned that quality of care and cost containment are a trade-off. That is, that efforts to contain costs inevitably result in lower quality of care. The relation between cost containment and quality of care is often poorly understood. It is probably more true that poor quality is expensive and improvement in quality can reduce costs[47].

Combined multifactorial prevention might be superior to solitary cholesterol-lowering intervention from the cost-effectiveness point of view. A Swedish study on two different cholesterol programmes in primary health care concluded that a low-intensity guideline programme was to be preferred from a cost-effective point of view[48]. The integration of a large scale Scandinavian prevention programme, aimed at serum cholesterol among other risk factors in primary health care, placed great demands for treatment and follow-up[49]. Still, combined multifactorial prevention, showing cost-effectiveness ratios from £900 to £1500 per Year of Life Saved[50-52], might be more cost-effective than a solitary cholesterol-lowering intervention, since the risk to develop CHD increases in a multiplicative manner with the number of risk factors. Many adults who are currently candidates for cholesterol-lowering drug treatment might no longer need such therapy after receiving alternative interventions, which are less expensive and have a long-term safety record[53].

Health education given by the GP aimed at multiple risk factors in patients with CHD seems to generate favourable cost-effectiveness ratios[54]. Although absolute effects in risk reduction are small, the whole population approach might also be a favourable approach from a cost-effective point of view[55-58]. We think that a national nutritional policy is required to achieve the full impact in a general practice population of health education given by the GP aimed at serum cholesterol and other CHD risk factors.

To aid the confluence of the discussions on feasibility of the guidelines and the evidence base of the guidelines, we have listed a set of criteria for profitable screening programmes (Table 2). These criteria, which were derived from different sources[59-61], are used to reflect on the results of this thesis. Each criterion is valued with + / - / ± / ? on the basis of the results of this thesis. If the cholesterol guidelines are checked against these criteria, many remarks have to be made.
Early diagnosis should improve the clinical outcome in terms of survival, and quality of life (criterion 2); the latest 'statin' trials show that early diagnosis improves the clinical outcome in terms of survival (WOSCOPS). Nothing is known yet about improvement in the quality of life outcome. The psychological effects of cholesterol lowering need consideration. Consensus should exist about whom to select for the screening programme (criterion 3); Although consensus seems to exist about intervening in patients with coronary heart disease, there is controversy about the need for screening in healthy persons. The use of the test should be feasible, and acceptable for the population (criterion 5); this seems true, even more so now that the desk top test devices are available.

TABLE 2. CRITERIA FOR BENEFICIAL SCREENING PROGRAMMES

1.	It concerns a serious health problem, given the clinical manifestations and the frequency of the disease	+
2.	Early diagnosis improves the clinical outcome in terms of survival, and quality of life	?
3.	Consensus exists about whom to select for the screening programme	±
4.	The screening test is acceptable regarding costs, accurateness and safety	+
5.	The use of the test is feasible, and acceptable for the population	+
6.	The screening strategy is feasible and effective	-
7.	The treatment is effective	±
8.	The treatment is acceptable and safe, without undesirable side-effects	?
9.	Positive screenees comply with subsequent advice and interventions	-
10.	Time and facilities for diagnosis and long-term treatment are available for positive screenees	±
11.	The costs of the screening programme show a favourable economic relation with possible costs of medical care arising from the screening programme	±

But the compliance from the doctor's side with repeat testing is nearly zero. The combination of the increase in quantity of cholesterol testing with the decrease in the quality of the diagnostic procedures is a matter of concern. The screening strategy should be effective (criterion 6); the targeting of cholesterol testing to those with positive risk profiles (the selective case finding) needs much improvement before the screening strategy can be

considered effective. The treatment should be effective (criterion 7); this is proven for patients with symptoms of CHD, but there are doubts for other patients. The treatment should be acceptable and safe, without undesirable side-effects (criterion 8); cholesterol-lowering diet and drug therapy seems acceptable and safe, but safety on the long-term has not been assessed yet for the new generation drugs. Positive screenees should be compliant with subsequent advice and interventions (criterion 9); positive screenees lack compliance to diet therapy. Time and facilities for diagnosis and long-term treatment should be available for positive screenees (criterion 10); it is not clear whether GPs will take time for long-term guidance for diet therapy. The costs of the screening programme should be in balance with possible costs of medical care arising from the screening programme (criterion 11); there is a lack of good quality information on cost-effectiveness of cholesterol lowering in general practice. The costs of the screening programme do not seem to be cost-effective for screening in persons without symptoms of CHD, especially women.

It is clear that focusing cholesterol testing on a well-described selective subgroup of patients for whom effectiveness or cost-effectiveness is favourable will have a positive effect on both the scientific value as well as the feasibility of the guidelines.

Conclusions and recommendations

Recommendations for updating and implementation of the DCGP cholesterol guidelines

The indications for cholesterol testing can be restricted. Cholesterol testing seems to be rational for patients with symptoms of coronary heart disease (survivors of CHD - or persons with symptomatic coronary stenosis - and total cholesterol > 5.5 mmol/l) and patients with symptoms of familial hypercholesterolaemia. Considering the unfavourable cost-effectiveness ratio and the low feasibility of selective case finding based on the coronary risk profile, caution is needed in screening persons without CHD. The usefulness of risk tables to target individuals with multiple cardiac risk factors (e.g. the Sheffield risk tables) needs further clarification.

Repeat testing in order to diagnose hypercholesterolaemia is important. GPs should comply with this guideline. Through restriction of the number of indications for cholesterol testing, and therefore in the number of patients to be tested, repeat testing will become more feasible.

The management algorithm described in the cholesterol guidelines (see page 137) can be simplified. Its complexity reflects the compromise between testing many persons and then trying to encourage diet therapy but to limit drug therapy. A more restrictive screening strategy justifies a less restrictive drug policy.

GPs should be more prepared to deal and instructed in dealing with patients who actively ask for testing, and be supported in this matter by patient education materials, preferably including the number-needed-to-treat tables.

The lack of motivation for prevention mentioned by many GPs and their hesitation to interfere in patients' lifestyle is a sign that primary prevention of CHD cannot be the task of GPs alone. A supportive public health approach is needed, with strategies like educating youngsters about the relation between lifestyle and the risk of CHD, and a proper reimbursement policy. The preventive approach of the general practitioner should be integrated into a broad strategy of preventive activities.

An integrated standard for prevention of (recurrent) coronary heart disease is needed from a scientific point of view, and will probably lead to higher adherence than the separate hypertension and cholesterol guidelines which now co-exist.

Recommendations for guideline development and implementation, and further research

More attention should be given to the feasibility of guidelines in daily practice during the process of their development, especially in guidelines with a controversial character.

It is of great importance to have a balance in the members of the working group which is responsible for the development of a guideline on a certain medical intervention. Balance in the composition of the working group has to be sought between believers and non-believers of the need for this intervention. Often guideline working groups are composed of believers only, because they are keen in volunteering and participating in the group and want to see their beliefs expressed in the guideline.

The need for collaboration in summarising the evidence in a raw format is high. Therefore all efforts have to be made to make the Cochrane Collaboration work. Evidence statements, such as Cochrane Collaboration reviews, should routinely include accessible presentation of treatment outcomes on benefit (e.g. quality adjusted years of life gained), hazard (e.g. number needed to treat, unwanted side-effects), and costs for a range of absolute risks.

More research is needed on implementation of practice guidelines, which include clear presentation of treatment outcomes on benefit, hazard, and costs for a range of absolute risks, and which are adapted by the GPs themselves in their own localised consensus procedure. With the aid of these measures patients should be enabled to weigh the benefits and hazards of intervention in their particular circumstances, and to choose the most preferable treatment option together with their doctor.

Behaviour-changing strategies are time and energy consuming. They should be used only for the implementation of clear-cut guidelines of high scientific validity (level I evidence) with a favourable cost-effectiveness balance.
Moreover, more research is needed on the amount of overall costs that are needed to execute implementation strategies. Comprehensive measures, like the cost-benefit ratio per GP who changed his/her behaviour in the right direction, need to be developed.

In the evaluation of the feasibility of a practice guideline, opinions on feasibility of both GPs and patients should be considered.

There is a need for economic evaluation of intervening in persons without CHD on their coronary risk. All relevant costs and benefits have to be considered, and community effectiveness and intangible costs have to be taken into account.

Standardisation of economic evaluations must have high priority in future economic evaluations. Further research is indicated on the value of a method for grading health care recommendations in which a threshold number needed to treat is calculated.

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Appendix 1

Dutch College of General Practitioners standard M20

DCGP-Standard Cholesterol

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Summary DCGP STANDARD CHOLESTEROL

Concepts

* a serum cholesterol level > 5.0 mmol/l is not a disease but rather one of the risk factors for coronary heart disease (CHD); it is not a risk factor for other vascular disorders
* categories for hypercholesterolaemia: 5.1–6.4 mmol/l, 6.5–7.9 mmol/l, ≥ 8.0 mmol/l

Detection

No general screening. Only for visitors to surgery of 18-65 years **known** to have:
- phenomena associated with a familial form of hypercholesterolaemia (xanthomas, corneal arcus or xanthelasmata < 40 years; lipaemic serum in fasting patient)
- CHD in history
- CHD among parents/siblings < 60 years
- hypertension
- diabetes mellitus
- familial hyperlipidaemia

Smoking alone is no reason for a cholesterol test

Diagnosis

Determine non-fasting serum cholesterol according to scheme; 1–2 week interval. Base value is mean of 2 or 3 measurements.

First measurement	≤ 5.0 mmol/l	do not repeat
	> 5.0 mmol/l	repeat
Mean 1st & 2nd measurements	≤ 6.5 mmol/l	do not repeat
	> 6.5 mmol/l	repeat

History	*	other risk factors for cardiovascular diseases
	*	composition of diet (also alcohol consumption)
Physical examination	*	xanthomas; xanthelasmata and/or corneal arcus < 40 years
	*	blood pressure
Supplementary examination	*	if suspicion of underlying cause (liver disease, hypothyroidism, diabetes mellitus): ALAT, τ-GT, TSH, glucose (fasting or 2 hours after loading)

Management

Chol < 6.5 mmol/l:	single advice, no follow-up
Chol > 10.0 mmol/l:	consult specialist
Chol 6.5–10.0 mmol/l:	advice or nutritional advice from dietician sufficient

Consider possible medicative therapy after 6 or 12 months treatment with advice in cases where:
- serumchol 6.5–7.9 mmol/l and ≥ 2 risk factors
- serumchol 8.0–10.0 mmol/l and ≥ 1 risk factor(s)

Non-medicative treatment
* education on elevated serumchol and risk factors for cardiovascular diseases
* stop smoking
* nutritional advice: support with brochures (O&O, Educational Bureau for Nutrition)
  - once by G.P. or assistant
  - guidance by G.P. or assistant once every 2 to 3 months
  - guidance by dietician
* reduce weight to a Quetelet index < 25

During check-ups: determine serumcholesterol; once only, unless result gives occasion for a change of therapy. Then repeat according to scheme given in Diagnosis section.

Management during the first 6 months

Serumchol 6.5–10.0 mmol/l: nutritional advice with guidance; check serumchol after 6 months

Management after 6 months' nutritional advice

Serumchol after 6 mths	risk factors[1]	management	serumchol after 12 months	management[3]
<6.5	not relevant	nutritional advice	not relevant	annual check up
6.5–7.9	0–1	nutritional advice + guidance	< 8.0	continue
			8.0–10.0	dietician possibly + medication[2]
	≥ 2	dietician possibly + medication[2]	< 6.5	continue
			≥ 6.5	reconsider medication[2]
8.0–10.0	0	nutritional advice + guidance	< 8.0	continue
			8.0–10.0	possible dietician
	≥ 1	dietician possibly + medication[2]	< 8.0	continue
			8.0–10.0	reconsider medication[2]

[1] additional risk factors: phenomena associated with familial form of hypercholesterolaemia, presence of CHD in patient and/or among parents/siblings < 60 years, hypertension, diabetes mellitus

[2] females without familial hypercholesterolaemia derive little benefit from medicative treatment

[3] annual check-up; if medication used: see checks under Medicative therapy

Medicative therapy

* continue nutritional advice
* determine HDL and triglyceride levels (high HDL: less strict indication for drugs: high trig.: indication for fibrates)
* if patient responds well to medication: annual check-up

First/second choice (equal value): Bile acid binding resins (10% decrease in serumchol; frequent gastrointestinal side-effects; influence resorption of other medicines; favorable effect on CHD proven). Colestipol (Colestid®) 4–6 x 5g sachets in 2 doses dd or colestyramine (Questran®) 3–4 sachets x 4 g in 2 doses dd.

Serumchol after 1 month: < 8.0 mmol/l continue

≥ 8.0 mmol/l consider cholesterol synthesis inhibitor

Cholesterol synthesis inhibitors (30% decrease in serumchol: side-effects: impaired hepatic function, myositis; long-term side-effects as yet unknown; favorable effect on CHD not proven at present); Pravastatin (Selektine®) 1 dd 10 mg or simvastatin (Zocor®) 1 dd 10 mg. Determine ALAT baseline value; after 1 month check serumchol and ALAT, when myalgia CPK also.

Serumchol after 1 month:

< 6.5 mmol/l continue, single check of serumchol after 6 months, annually thereafter

≥ 6.5 mmol/l increase dose in step-wise fashion to max. 40 mg dd; monthly check until serumchol < 6.5 mmol/l

At a dose of 40 mg and serumchol ≥ 8.0 mmol/l add bile acid binding resin. If elevation persists: consult specialist.

If ALAT remains elevated (more than three times upper limit): cease medication.

Annual check-ups

* discuss: nutritional advice, use of medication and changes in risk factors
* determine: serumchol; once only unless result gives occasion for change of therapy

Specialist consultation

* serumchol > 10.0 mmol/l
* serumchol ≥ 8.0 mmol/l despite dietary measures and medicative therapy

Introduction

An increased serum cholesterol level is one of the risk factors for coronary heart disease (CHD). The term CHD in this standard indicates conditions caused by ischaemia of the myocardium based on coronary sclerosis (angina pectoris and myocardial infarction). It has not been demonstrated that an increased serum cholesterol level forms a risk factor for other vascular conditions. The cholesterol standard contains guidelines for the detection, diagnosis and treatment of hypercholesterolaemia in persons between 18 and 65 years old. The upper limit of 65 years has been chosen because in the elderly the importance of an increased serum cholesterol level as a risk factor gradually declines. Furthermore, there is a lack of good intervention studies in this age group. The prevention of hypercholesterolaemia and the treatment of conditions that may be caused by hypercholesterolaemia fall outside the area of this standard.

General health education programmes can achieve a reduction of 5% in the mean serum cholesterol level of the population. This reduction at population level is the most cost effective, but it does not belong to the tasks of the GP. A supplementary, individual approach is desirable since, even with health education, an important percentage of the population will retain a high serum cholesterol level. GPs are regularly confronted with a request for a cholesterol test, or with a cholesterol value that has been determined elsewhere. There are also a number of new developments, such as the introduction of powerful cholesterol-lowering drugs, the cholesterol synthesis inhibitors, and the arrival in general practice of serviceable test equipment for the determination of cholesterol. There is doubt among GPs about the sense of treating the large group of patients who have a moderately elevated serum cholesterol level, as encountered in general practice. All this means that it is necessary to formulate a standpoint for general practice on the detection and possible treatment of an elevated serum cholesterol level. This standard formulates guidelines which are at the same time intended to prevent over-treatment.

The Central Liaison Organ for Intercollegiate Assessment (CBO) has recently had occasion to revise the 1987 Consensus on Cholesterol. This offers a good opportunity for the publication of a DCGP-Standard on Cholesterol which takes as much account as possible of the revision.

Physiology

Cholesterol is a compound which is naturally present in the body and which is important in the composition of the cell membrane and in the formation of sex and adrenal hormones, vitamin D and bile acids. The blood cholesterol level is determined in part by genetic factors and partly by the quantity of fat and cholesterol in the diet. The majority of cholesterol in the blood is synthesized in the liver, the rest being drawn from the diet. Fats in the diet mainly consist of triglycerides, together with phospholipids and cholesterol.

The following lipoproteins (fat transporting proteins) may be distinguished in the serum: chylomicrons, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high density lipoprotein (HDL). Chylomicrons and VLDL are rich in triglycerides; LDL and HDL are rich in cholesterol. The LDL forms the most important atherogenic fraction. Of the total serum cholesterol, 60–70% is determined by the concentration of LDL. The HDL contain 20–30%, and the VLDL 10–15% of the total serum cholesterol. The LDL take care of the cholesterol transport from the liver to the peripheral tissues. By contrast, the HDL transport excess cholesterol from the peripheral tissues to the liver. The HDL form a protective factor against CHD.

The most important determinant of the serum cholesterol level and the harmful LDL fraction is not the amount of cholesterol, but rather the amount of saturated fat in the diet. The ratio of unsaturated and saturated fats in the diet has a particular significance. The HDL level is increased by, amongst others, physical examination, weight reduction and moderate alcohol consumption (a maximum of two units per day), and it is lowered by smoking.

The patient's input

The DCGP Standards give guidelines for the GP's daily work; the GP's role is thus the focus of attention. But, of course, patient-related factors contribute to the management of the case. For practical reasons this perspective is not always repeated in the guidelines, but is mentioned here explicitly. Where possible the GP determines on his management of the case in a dialogue with the patient, taking account of his specific circumstances and with a recognition of the patients' own responsibility, for which adequate information is a precondition.

The GP's considerations

The personal insight of the doctor, of course, is an important aspect in all guidelines. Consideration of the relevant factors in a concrete situation can justify a considered departure form the management described here. This does not mean, however, that the standard is not intended to function as a measure and a guide.

Classification of serum cholesterol levels and epidemiology

A high serum cholesterol level is not a disease but one of the risk factors for CHD. The importance of cholesterol as a risk factor increases gradually with an increase in the serum cholesterol level. No clear boundary can therefore be drawn between a normal and an abnormal blood cholesterol level. When drawing up guidelines, however, clear limiting points have to be chosen. In this regard, the present standard agrees with the CBO Consensus on Cholesterol (1991) in which the serum cholesterol level is divided into the following four categories, for both males and females from 18 to 65 years old:

≤ 5.0 mmol/l	5.1–6.4 mmol/l	6.5–7.9 mmol/l	≥ 8.0 mmol/l

A serum cholesterol level above 5.0 mmol/l is regarded as elevated.

The predictive value of an elevated serum cholesterol level for CHD in the most commonly occurring category (between 5.0 and 8.0 mmol/l) is low for the individual and differs between males and females. More than 60% of all myocardial infarctions occur in persons who have a serum cholesterol level that is lower than 6.5 mmol/l. The mean serum cholesterol of persons who suffer from a CHD is 6.3 mmol/l. The mean level for persons who remain free of CHD is 5.7 mmol/l. In the absence of any other risk factors, 45-year-old males with a serum cholesterol level of 8.0 mmol/l have a chance that is four times as high of developing a CHD within six years than females of the same age. The absolute risks are small for both sexes, but increase with age. If other risk factors are present, the risk of CHD increases greatly for both sexes, increasing more for males than females. As age increases, for both males and females, a steadily smaller number of mortalities can be explained on the basis of serum cholesterol level since other diseases start to play a role. Patients with familial hyperlipidaemia can experience atherosclerosis and xanthomas in childhood, and there is an increased probability of developing CHD in youth.

In the Dutch population in the age group 20-60 years, 20% of the males and 17% of the females have a serum cholesterol of 6.5 mmol/l or higher. Among males the percentage having a serum cholesterol greater than 6.5 mmol/l increases more or less linearly from 3% in the age group 20–29 years to 30% in the age group 50–59 years. In females the percentage increases from 5% in the age group 20–29 years to 14% among the 40–49-year age group, increasing to 39% in the 50–59-year age group. This last figure is connected with the cessation of ovarian oestrogen production. Familial hypercholesterolaemia with extremely high cholesterol levels (homozygotes 15–30 mmol/l, heterozygotes 8–14 mmol/l) and a greatly increased LDL level occurs in 0.2% of the population.

Effects of influencing cholesterol levels

Intervention studies have been conducted virtually exclusively on middle-aged males with a highly elevated serum cholesterol. The effect of cholesterol reduction on the morbidity and mortality of CHD among other age groups and among women has not been sufficiently investigated. The results of clinical intervention studies cannot be simply extrapolated to the population of general practice. The participants in such studies have a better motivation to stick to a diet or medication than the average patient. In cases of elevated serum cholesterol a diet, accompanied by guidance, gives a reduction in the serum cholesterol level of approximately 10%. The classic medications achieve a similar reduction. With the aid of the cholesterol synthesis inhibitors the serum cholesterol level can be reduced by approximately 30%. However, no intervention studies have yet been published on these new drugs that demonstrate the effects on the morbidity and mortality from CHD.

The effects on mortality of a lowering of cholesterol are limited. Treatment with classical cholesterol-lowering agents plus diet gives a reduction of about 20% (from approximately 10% to approximately 8%) in the occurrence of a myocardial infarction (fatal or not) within seven years among middle-aged males with a serum cholesterol level of 7.5 mmol/l. The chance of not developing CHD thereby rises from 90 to 92%.

Since the cholesterol synthesis inhibitors reduce the serum cholesterol level more strongly, it may be theoretically expected that there is a greater effect on the prevention of CHD. It has thus been calculated that, for 100 45-year-old males with a serum cholesterol level of 8.0 mmol/l, a 32% reduction of serum cholesterol level will lead to the prevention of a myocardial infarction in 10 males after 20 years of treatment; 13 males will still experience a myocardial infarction despite treatment.

The number of myocardial infarctions declines as a result of lowering of the serum cholesterol level, but, in contrast to what might be expected, this is not accompanied by a reduction in total mortality. An as yet unexplained increase in mortality occurs as a result of accidents, murder, suicide and, to a lesser degree, cancer. The effects of a lowering of the serum cholesterol level on non-cardiac morbidity have virtually never been investigated. This information lead the working group to adopt a measure of reserve in drafting the guidelines for the detection and treatment of persons having an increased serum cholesterol level.

Guidelines

For the detection and guidance of persons with an elevated serum cholesterol level the GP should possess the following:

- a patient record system which is suitable for the systematic noting of the patient's risk factors (hypertension, smoking, diabetes mellitus and the family history (parents, siblings) with reference to CHD prior to the 60th year of life);
- the Advisory Guidelines on Good Nutrition and educational pamphlets on hypercholesterolaemia, hypertension and smoking from the Educational Bureau for Nutrition.

The GP can delegate part of the detection and guidance of persons with an elevated serum cholesterol level; he/she should then have available well-educated and well-instructed assistance from someone who has the time and facilities to perform this task.

Detection

For reasons of practicability and the expected benefit, this standard recommends cholesterol testing of visitors to the surgery in the age group 18-65 years who have one or more of the following characteristics:

- phenomena associated with the familial form of hypercholesterolaemia;
  - xanthomas;
  - xanthelasmata and/or corneal arcus prior to the 40th year of life;
  - cloudy (lipaemic) serum in fasting circumstances.
- the presence of:
  - CHD;
  - CHD in first-degree relatives (parents, siblings) prior to the 60th year of life;
  - hypertension;
  - diabetes mellitus;
  - familial hyperlipidaemia (FH). The GP should consider FH if much CHD in the family, or CHD at a youthful age occurs, or if a relative has an extremely elevated serum cholesterol level (>10 mmol/l).

Other risk factors for cardiovascular diseases, especially a Quetelet index > 30, smoking, and too little physical exercise, demonstrate insufficient correlation with an elevated serum cholesterol level, or else are too weak as risk factors to be used as leads in detection. No recommendation is made in the present standard on the determination of serum cholesterol levels of persons who only have smoking as risk factor. Since the contribution of cessation of smoking to the reduction of risk of CHD is almost always larger than that of a cholesterol-reducing treatment, smoking alone is no reason for determining the serum cholesterol level. Such persons are advised to cease smoking first.

For patients who do not fulfil the above criteria and who request the determination of their serum cholesterol level on their own initiative, it is important that the GP inquires why the patient wishes to have his or her serum cholesterol level checked, and advises the patient, in association with the request for help, about why a check is not indicated according to the current guidelines. No guidelines are given on whether or not to grant such a request.

Diagnostic guidelines

As a consequence of the great biological variation of the serum cholesterol level, a single measurement is not sufficient to determine it reliably. Three measurements are necessary, taken at intervals of one to two weeks. The mean of these is taken. Fewer measurements are only appropriate if the first one produces a low result, or if the first two measurements produce a low average. The patient does not have to be fasting for the determination of the total serum cholesterol. The HDL cholesterol and triglyceride levels are only determined if medicative therapy has been decided upon. The patient should be fasting for the latter determination. The following procedure is followed:

first measurement	≤ 5 mmol/l $\rightarrow$ do not repeat > 5 mmol/l $\rightarrow$ repeat measurement
average of first and second measurements	< 6.5 mmol/l $\rightarrow$ do not repeat ≥ 6.5 mmol/l $\rightarrow$ repeat measurement
third measurement	the mean of these (maximally three) measurements is the base level

If a serum cholesterol level ≥ 6.5 mmol/l is found a further history is taken and further examination is undertaken. Equipment for the determination of cholesterol in general practice has recently become available. Provided the personnel who use the equipment are well trained, and the equipment is well maintained and regularly standardized, the reliability seems to be good. At this time insufficient data are available on its usefulness, and its reliability can only be guaranteed at

the expense of a great deal of attention and cost. The use of such equipment is therefore not recommended.

History taking: The presence of other risk factors for cardiovascular disease (hypertension, diabetes mellitus, CHD, smoking, overweight, little physical exercise, CHD among first degree relatives) are inquired into once again. An elevated serum cholesterol level may occur as a result of alcohol abuse, diabetes mellitus, hypothyroidism and liver diseases. It is ascertained whether there are indications for such an infrequently occurring cause. The GP forms an impression of how far the daily nutritional pattern corresponds with the Guidelines on Good Nutrition.

Physical examination: Inquiries are made as to whether the patient has any indication of a familial form of hypercholesterolaemia. Xanthomas are sought, and xanthelasmata and a corneal arcus in patients younger than 40 years old. If it is not yet known, the blood pressure is measured.

Supplementary examination: If the suspicion exists of one of the underlying causes mentioned above, then the blood sugar level (fasting or 2 hours after loading), the ALAT (SGOT), τ-GT or TSH are determined.

Consultation: In suspicion of familial hyperlipidaemia (serum cholesterol > 10.0 mmol/l) the patient is referred to an internist for definitive classification. No recommendations are made in the present standard about the management of children of patients with this disorder.

Treatment guidelines

Before initiating drug treatment of a hypercholesterolaemic patient, the patient's other risk factors come into consideration for advice and treatment.

Education: Education upon the significance of an elevated serum cholesterol level is extremely important because determination of an elevated serum cholesterol level can affect the patient's experience of his or her health. During the counseling it is ascertained what the patient already knows about cholesterol and about the consequences of an elevated serum cholesterol level. The following aspects are dealt with (if necessary spread over a number of consultations):

- the reason for the (repeated) measurement of the cholesterol value;
- the cause of an elevated serum cholesterol level and the factors that influence it;
- the consequences of hypercholesterolaemia;
- the importance of other risk factors and the place of hypercholesterolaemia therein;
- the goal and the manner of treatment, the importance of check-ups and compliance with therapy;
- the importance of adapting one's life and habits in order to influence other possible risk factors;
- the effects that may be expected from the treatment, and the possible side-effects of medicative treatment;
- the patient's choice to let him or herself be treated or not.

In the first place nutritional advice is provided according to the 'Guidelines on Good Nutrition' (GGN), regardless of the number of risk factors. Smokers are urged to cease smoking, since the effect of cessation of smoking upon the prevention of CHD is greater than the effect of lowering cholesterol.

The serum cholesterol level is determined during the check-ups in schemes 1, 2 and 3. This determination is performed once only, unless the value found provides grounds for changing the therapy. In this case the triple determination scheme described in the Diagnostic Guidelines is followed. During the treatment one attempts to achieve a reduction of the serum cholesterol to ≤ 6.5 mmol/l. This target value will not, however, always be achieved. This can be accepted, provided there are no indications for medicative therapy.

SCHEME 1. MANAGEMENT IN THE FIRST SIX MONTHS.

Cholesterol level (mmol/l)	**Management**
5.1–6.4	Nutritional advice according to GGN. Check-up not necessary.
6.5–10.0	Nutritional advice according to GGN with guidance. Check-up after 6 months, and then scheme 2.

Since the effect of giving nutritional advice without any form of guidance is limited, the GP or the assistant discusses the nutritional advice with the patient once every two to three months.

SCHEME 2. MANAGEMENT AFTER SIX MONTHS.

Cholesterol level	**Additional risk factors****	**Management**
< 6.5	-	Nutritional advice according to GGN. Annual check-up.
6.5–7.9	0–1	Nutritional advice according to GGN. Check-up at 6 mths, then scheme 3.
	≥ 2	Dietary advice from dietician. Check-up after 6 months, then scheme 3. Possible medication*, depending on the severity of the individual risk factors. Check-up: see Medicative Therapy.
8.0–10.0	0	GGN nutritional advice according with guidance. Check-up after 6 months, then scheme 3.
	≥ 1	Dietary advice by dietician. Check-up after 6 months, then scheme 3. Possible medication*, depending on the severity of the individual risk factors. Check-up: see Medicative Therapy.

SCHEME 3. TREATMENT AFTER TWELVE MONTHS.

Cholesterol level after 6 mths	**Additional risk factors****	**Cholesterol level after 12 mths**	**Management**
6.5–7.9	0–1	< 8.0	Continue GGN nutritional advice. Annual check-up.
		8.0–10.0	Treat according to scheme 2.
6.5–7.9	≥ 2	< 6.5	Continue management. Annual check-up.
		≥ 6.5	Reconsider medication*.
8.0–10.0	0	< 8.0	Continue GGN nutritional advice. Annual check-up.
		8.0–10.0	Continue GGN nutritional advice. If necessary refer to dietician. Annual check-up.
8.0–10.0	≥ 1	< 8.0	Continue GGN nutritional advice. Annual check-up.
		8.0–10.0	Reconsider medication*.

* Females without familial hypercholesterolaemia will gain relatively little benefit from medical treatment, which is indicated only in the presence of serious associated risk factors.

** Risk factors are: phenomena associated with a familial form of hypercholesterolaemia; presence of CHD; CHD in parents/siblings prior to the 60th year of life; hypertension; diabetes mellitus. Smoking is not counted as an additional risk factor in the present standard.

Non-drug advice

The basis of the non-medicative advice is formed by the nutritional advice, which follows from what is currently accepted as healthy nutrition. This advice remains very important, also ifmedicative therapy is undertaken. The nutritional advice is described in the Guidelines on Good Nutrition of the Council for Nutrition. This offers the GP a good framework within which he or she can tune the advice to the individual patient. Dietary advice in cases of elevated serum cholesterol levels is characterised by a limitation of the total amount of fat in the diet, and of the proportion of saturated fats therein. This is compensated by an increase in the proportion of complex carbohydrates. Guidance by the GP, assistant or dietician in the change of nutritional habits produces a better result than merely giving the patient a diet brochure.

Alcohol use should be limited to a maximum of two units per day. Moderate alcohol use may effect a limited increase in HDL cholesterol. Consumption in larger amounts increases the triglyceride level. Overweight unfavorably influences the serum lipoprotein pattern and is frequently accompanied by a lowered HDL level. A Quetelet index < 25 should be aimed for. The consumption of coffee does not elevate the serum cholesterol level, except when it is consumed in large amounts in the form of unfiltered coffee ("backwoods coffee"). Vitamin E, wheat germ oil, evening primrose oil, fish oil, lecithin, bran and garlic have not been shown to have a noticeable influence on the serum cholesterol or triglyceride levels.

Drug therapy

There are at present two groups of compounds available for the medicative treatment of an elevated serum cholesterol level: the bile acid binding resins and the cholesterol synthesis inhibitors. Substances such as neomycin, dextro-thyroxine and estrogens are no longer indicated due to their side-effects or limited effectiveness. If medicative therapy has been decided on, then the triglyceride and HDL levels are determined. If elevated triglyceride levels are present bile acid binding resins are contraindicated and fibrates (clofibrate: generic, Clofi-ICN®; gemfibrozil: Lopid®) are a first choice. The HDL level is important for the group of persons with a serum cholesterol level between 6.5–7.9 mmol/l. An elevated HDL level affords relative protection against CHD and reduces the need for medicative treatment. Nicotinic acid compounds are often poorly tolerated. Fibrates are indicated in certain forms of familial lipoproteinaemias.

The cholesterol synthesis inhibitors lower the serum cholesterol level more, about 30%, than the bile acid binding resins, and they are easier to administer. As far as is currently known, they have limited side-effects. It has, however, not yet been demonstrated that they also prevent CHD. The consequences of the long-term use of cholesterol synthesis inhibitors are not yet known. The bile acid binding resins lower the serum cholesterol level by approximately 10%. Gastrointestinal side-effects, such as constipation, occur regularly, and bile acid binding resins can inhibit the resorption of other medicaments. Their unpleasant taste is inclined to result in side-effects such as nausea. It has been demonstrated that the bile acid binding resins lower the morbidity and mortality from CHD. Based on the above, the GP determines the therapy of choice together with the patient who is eligible for treatment.

Cholesterol synthesis inhibitors:

Contraindications for the use of these compounds are pregnancy and lactation. The cholesterol synthesis inhibitors may only be used by females in the fertile period in association with contraceptive measures. The ALAT is determined prior to the initiation of the therapy. This test is repeated at the check-up after four weeks. The therapy is terminated in case of an elevation of more than three times the normal upper limit.

Therapy is initiated with 1 dd 10 mg simvastatin (Zocor®) or pravastatin (Selektine®) for four weeks, taken in the evening. A check-up is performed after four weeks. This includes the

determination of the serum cholesterol level and the ALAT. If the patient complaints of myalgia the CPK is also determined. Inquiries are made into side-effects. If the serum cholesterol level is < 6.5 mmol/l then the management continues unchanged. The serum cholesterol level is determined once after six months and then annually. A single determination is sufficient, unless the value found gives occasion for a change of therapy. In this case the triple determination scheme described under Diagnostic Guidelines is followed.

In an average serum cholesterol level of ≥ 6.5 mmol/l the dosage is increased by 10 mg and the procedure is repeated. If in repeated determination the average serum cholesterol is ≥ 6.5 mmol/l during the use of 20 mg simvastatin or pravastatin, then the dosage is increased to 40 mg. If the serum cholesterol is < 8.0 mmol/l thereafter, then the use of 40 mg is continued. If the level remains ≥ 8.0 mmol/l, then adding a bile acid binding resin is considered. If the serum cholesterol level remains elevated, then a specialist consultation follows.

Bile acid binding resins:
Treatment is initiated with 3 to 4 sachets of colestyramine (Questran®) or 4 to 6 sachets colestipol (Colestid®) per day, in two doses, dissolved in fluid. A check-up is made after one month, in which the serum cholesterol level is determined. A single determination is sufficient, unless the value found gives occasion for a change of therapy. In this case the triple determination scheme described under Diagnostic Guidelines is followed. An inquiry is made into possible side-effects. During initiation and follow-up one checks whether there are any interactions with other medicaments (in particular oral anticoagulants and oral antidiabetics). If the serum cholesterol level is < 8.0 mmol/l, then the use is continued. If the level is ≥ 8.0 mmol/l, then the use of a cholesterol synthesis inhibitor is contemplated.

Check-ups and referral
During the annual check-ups inquiries are made into the compliance with dietary advice and use of the medication. At the same time a check is made whether there has been any change in the patient's risk factors. The serum cholesterol level is determined. A single determination is sufficient, unless the value found gives occasion for a change of therapy. In this case the triple determination scheme described under Diagnostic Guidelines is followed. At this time there are insufficient data available to determine whether or not medication can be discontinued on the long term.

If, despite dietary measures and medicative therapy, the serum cholesterol level does not fall below 8.0 mmol/l within one year, then is it desirable to consult a specialist.

Origin

In November 1990 a working group of six doctors with a more than average expertise in the field of cholesterol was assembled. The working group consisted of the GPs Dr. J.J. van Binsbergen, A. Brouwer, B.B. van Drenth, A.F.M. Haverkort, Dr. A. Prins, and the physician T. van der Weijden. The basis for the standard was the draft of the revised version of the CBO-Consensus on Cholesterol of 1991. The working group wrote a concept standard in a short time.

In May comments were requested from 100 GPs whose addresses were selected at random from the DCGP membership list. 51 commentary forms were returned. Apart from that, a conference was held in June 1991 in connection with the Cholesterol standard. At the conference GPs and other experts spoke upon six propositions related to crucial points in the standard. A variety of comments were also received from different sources. The concept standard was assessed once again by the working group on basis of the comments received and the results of the conference, and a number of changes were introduced.

Appendix 2

Systematic development of an implementation programme for cholesterol guidelines. Description of the intervention.

Introduction

This appendix illustrates the application of a general model for development of a programme for improvement of working according to guidelines[1]. A combination of several implementation strategies, linked to the barriers to adhere to the guidelines is advocated[2 3]. Several theories about the development of behaviour change programmes for physicians are mentioned in the literature[4-6]. Three major groups of factors are regarded as affecting behaviour: predisposing factors (e.g. knowledge, attitudes) which predispose an individual to take action, enabling factors (e.g. skills) which enable a particular behaviour to occur, and reinforcing factors (e.g. attitudes of peers) which reinforce and tend to maintain new behaviours. For each of the multiple predisposing, enabling, and reinforcing factors identified, a specific component of a comprehensive behavioural change programme for physicians must be provided. Such a programme should be a systematic coherent package that starts with identification of current behaviour on the subject, necessary improvements, and potential barriers to change. Interventions should be developed, applied in a plan for change using a comprehensive approach and organised at different levels.

To address the objectives of the programme for improvement the focus should lie on the barriers that seem to be most vulnerable for change. In the choice of optimal learning conditions a complex of effective methods should be emphasised, like feedback on actual performance, and repetition of the educational message through reminders, in combination with strategies such as small peer group discussions, outreach visits of academic detailers, or local opinion leaders[7 8].

Methods

The model used for the development of a programme for improvement can be summarised as follows: After assessment of barriers to change perceived by physicians, necessary changes for physician performance in relation to cholesterol management were identified. Each change was analysed according the predisposing, enabling and reinforcing factors and also into the components attitude, knowledge, skills, or practice organization. Then the most optimal learning conditions to promote achievement of each change were determined. The barriers to change most frequently mentioned were assessed using two data sources:

A) A questionnaire of the Dutch College of GPs (DCGP) was sent to a random sample of 100 members of the DCGP (response 52%)[9]. The GPs were asked to evaluate the significance of the proposed guidelines from medical and social points of view, and to consider feasibility.

B) A questionnaire to 32 interested GPs, participating in an implementation study of the cholesterol guidelines. The GPs were asked about current behaviour on cholesterol management, as well as their attitude towards the cholesterol guidelines.

Results

The barriers to change

The barriers to change that could be identified are listed in table 1. There is considerable lack of motivation because of doubts about effectiveness of cholesterol lowering, or because of GPs' hesitation to intervene in the patients' lifestyle and/or to induce fear. Other possibly important barriers are the lack of motivation for repetition of tests to diagnose hypercholesterolaemia, the problems GPs experience with diet therapy (lack of knowledge, patient compliance, or time), as well as the way of dealing with demanding patients.

The objectives of the educational intervention are listed in table 2. These objectives meet existing needs of education on cholesterol management[10]. Four different learning conditions were developed to cover the objectives defined; an educational group session, provision of supportive materials, feedback on performance, and face-to-face instruction.

The choice of learning conditions was influenced by focusing on the first section of the guidelines: gaining the right prevention attitude for selective case finding. Such a screening attitude will prevent unnecessary labelling and treatment.

A programme for improvement

The intervention is spread out over a period of 5 months (Table 3). This period is necessary for the provision of ongoing reinforcement of new behaviour by repetition of the educational message. Just before the actual programme for improvement starts, participating GPs have to register each

TABLE 1. BARRIERS TO CHANGE MENTIONED BY DUTCH GPS, TO WORKING ACCORDING TO CHOLESTEROL GUIDELINES.

General:
- Lack of motivation for preventive activities on coronary heart disease (CHD) because of doubts about efficiency and effectiveness, or hesitation to intervene in a patient's lifestyle, risking to induce fear (labelling) [A]*.
- Lack of counseling skills. Patients actively ask for cholesterol measurements or medication [A].
- The guidelines for Dutch GPs deviate on some aspects from those of Dutch specialists [A].

Case finding:
- Lack of a patient registration system in which patient data on (risk factors for) CHD can be found quickly [B]*. Difficulty to update data on CHD in first degree relatives < 60 years [A].
- Lack of physician compliance to the age criteria for case finding [B].
- Hesitation in quitting case finding on indications, well-known but not valid according to the guidelines: smoking, TIA/CVA in history, adipositas, claudicatio intermittens [A].

Diagnosis:
- Lack of motivation to use more than 2 tests for diagnosis of hypercholesterolaemia [B].
- Three measurements for diagnosis not feasible, and disturbing/ inconvenient for the patient; the cutoff point for repetition of the test is too low [A].
- Disagreement with referring a patient to a specialist in case of suspicion of Familiar Hypercholesterolaemia [B].

Therapy:
- Lack of expertise in prescription of an adequate cholesterol-lowering diet [A] [B].
- Lack of motivation for diet-therapy because of poor patient compliance. The patient prefers medication (which is often easily prescribed by specialists) [A].
- Prescribing and guiding diet therapy is considered too time-consuming [A].
- Difficulty to acquire good patient education materials as recommended in the guidelines [A] [B].
- Complexity of the management outline of the guidelines [A].

* The characters in brackets [A, B] correspond with the source of data through which the barrier was identified
[A]: data of DCGP questionnaire (52 GPs)
[B]: data of the baseline questionnaire of the implementation study of the cholesterol guidelines (32 GPs)

'cholesterol consultation' (cholesterol diagnosis and/or therapy was (one of) the subject(s) of the consultation) during a period of 8 weeks, in order to gain insight into their own performance. The registration form is designed to measure actual performance according to the guidelines.

Educational group session. The programme starts with an educational group session, chaired by a local CME experienced peer, and is composed of the following elements; feedback on registered patient contacts to gain insight into performance, a lecture with discussion (50 minutes), and a skills training (50 minutes). The lecture deals with the content of the guidelines itself and their scientific justification. The skills training contains three patient cases; a patient actively asking for a cholesterol test, a patient showing poor compliance on cholesterol-lowering diet, and a patient actively asking for medication. No more than six GPs participate at one time in a session. The GPs are tested on knowledge just before and after the session.

Providing educational materials. At the group session the GPs are given an outline of the guidelines with the supporting scientific report, and copies of educational sheets. In addition they receive a sufficient supply of the patient education materials recommended in the guidelines, as well as patient education materials especcially meant for the group of patients without an indication for case finding, a desktop flow chart of the guidelines, and a file with consultation registration-forms to support the self-audit and feedback procedure.

Self-audit, feedback on performance. The GPs are instructed to register 'cholesterol consultations' during or immediately after the consultation, or as soon as possible the very same day. This registration-form is designed to guide the GP as much as possible towards the guidelines. The GP is able to check the quality of a registered consultation; an abstract of the national guidelines is

TABLE 2. THE OBJECTIVES OF THE EDUCATIONAL PROGRAMME ON CHOLESTEROL GUIDELINES FOR GPS.

educational objective	factor/component	applied learning condition(s)
GPs should know about (cost-) effectiveness of cholesterol screening	predisposing factor/ knowledge, attitude	educational group session
GPs should test for cholesterol according to recommended age criteria and medical indications	predisposing factor/ knowledge	guided consultation registration, personal feedback, educational group session
GPs should be convinced of the importance to take three measurements for diagnosis	predisposing factor/ knowledge, attitude	educational group session, guided consultation registration, personal feedback
GPs should refer the patient to a specialist if FH is suspected	predisposing factor/ knowledge	guided consultation registration, educational group session
GPs should have a clear outline of the guidelines on therapy at their disposal	enabling factor/ practice organisation	provision of desk-top flow sheet of the guidelines
GPs should have a sufficient supply of the right patient education materials	enabling factor/ practice organisation	provision of patient education materials
GPs should comply with diet therapy before prescribing cholesterol-lowering drugs	enabling factor/ skills, knowledge	guided consultation registration, personal feedback
GPs should learn to deal with patients who actively ask for (non-indicated) cholesterol-determinations	reinforcing factor/ skills, attitude	educational group session (including skills training), personal feedback

TABLE 3. THE EDUCATIONAL INTERVENTION ON CHOLESTEROL GUIDELINES.

T-2 *(2 months before)*	non-guided self audit without feedback during a period of 8 weeks	
T0	educational group session:	- feedback on registered consultations - lecture with discussion - skills training
	provision of materials:	- the guidelines including full scientific report - copies of the educational material - 50 consultation registration-forms plus manual - desktop flow chart of the guidelines - sufficient supply of patient education materials
*T** *(continuing)*	guided self-audit and feedback; registration of cholesterol consultations with immediate feedback	
T1 *(after 1 month)*	face-to-face-education; discussing the flow chart of the guidelines materials given:	- recommendations for practice management
T3 *(after 3 months)*	face-to-face-education; feedback on registered consultations	

printed on the inside of the cover, so he or she can get immediate feedback on actual performance. The GPs register during a period of five months, in order to repeat the educational message. After two weeks of registering the GPs are contacted by phone and given further instructions if necessary. The GPs are reminded of registration by telephone-contact several times during the 5-month period.

Face-to-face instruction. After a period of at least four weeks all practices are visited for face-to-face instruction. In a one-hour session with the GP(s) of the practice the contents of the guidelines are discussed intensively by studying the desktop flow chart together. Special attention is given to the feasibility of the guidelines in daily practice. To encourage improvements of practice management, which may facilitate working according to the guidelines, the GPs are given written advice and recommendations for the structure of the patient registration system as well as the role of the practice assistant. If necessary, the GPs are given further instructions on the registration of cholesterol consultations. After another 8 weeks of registering cholesterol consultations the practices are visited for a second time. Again a one-hour session is held with the GPs. This time individual feedback is given on actual performance based on the registered consultations.

Discussion

Physicians' attitudes and motivation, rather than availability of practice guidelines, apparently relate more to actual preventive performance[11] [12]. Doctors have been educated primarily on caring for sick patients, not maintaining people healthy. Moreover there is no immediate benefit to the patient and no reward for the GP. Lack of time is a major reason for inappropriate case finding behaviour; care for patients who are ill prevails over preventive services. Financial support for preventive services might be a powerful inducement for changing behaviour, but this goes beyond educational intervention.

TABLE 4. PROGRAMMES FOR IMPROVEMENT OF CHOLESTEROL MANAGEMENT, AN OVERVIEW.

study	study aim	METHODS				MATERIALS			
		group education	feedback	reminder	other	self-study	desk-top	pat. education	other
reported study	compliance with DCGP guidelines	educational group session	face-to-face-education + feedback	registration of consultations		scientific report, educ. materials	desk-top flow chart	patient education materials	practice management tips
Mann 1990	systematic prevention	training session on counseling			easy access to dietitian + specialist	strategies for lifestyle changes	desk-top information	patient education materials	
Jack 1991	improvement of cholesterol management	training sessions on diagnostics + diet counseling	bimonthly feedback	patient-specific chart reminders	incentive gifts				newsletter articles
Reeder 1991	compliance with Can. guidelines	2 seminars on guidelines				scientific report	flow chart	patient education materials	list of local experts
Headrick 1992	compliance with NCEP guidelines	lecture		generic/patient-specific chart reminders					
Boyle 1992	compliance with NCEP guidelines	2-day workshop on diagnostics + diet counseling	feedback on technical performance			procedure manuals			diet assessment tool
Robbins 1993	compliance with NCEP guidelines			supportive computer software					
Rosser 1993	compliance with Can. guidelines					summary of the scientific report	wall flow chart	patient education materials	

Another barrier described in the literature is undermining of the credibility of guidelines by contradictory recommendations. This is applicable to the Dutch situation where the guidelines for Dutch GPs deviate on some aspects from the guidelines of the Dutch specialists. It was mentioned as a barrier to change (Table 1). Another barrier to change not directly addressed is the hesitation of a GP to intervene in a patient's lifestyle. It is possible that this hesitation is fed by lack of belief in effectiveness or safety of cholesterol intervention, or lack of belief in counseling and behaviour change skills.

Compared to various intervention programmes on cholesterol management[10 13 14 15 16 17 18], this study entails a rather comprehensive programme (Table 4). Only Mann et al. based their educational intervention on assessment of barriers to change and applied a systematic approach as was done in this project. Self-audit and feedback by guided consultation registration is not used in any other programme.

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Appendix 3

Characteristics of the trials included in chapter 7

Legend

* mean percentage difference in cholesterol reduction between treatment group(s) and placebo group during the trial

** only the double-blind group

\# percentage difference in cholesterol reduction between the groups after one year of treatment

\#\# drop-outs not included in number of patients

Primary prevention trials

Study author, publication year	Setting	Intervention treatment/control (doses per day)	Mean duration (yrs) (Post trial follow-up)
UNIFACTORIAL DIET			
Los Angeles VA Study Dayton 1969	domicilary care institution Los Angeles	chol-lowering diet/ usual diet	3.6 (2.0)
Minnesota Cor. Survey Frantz 1989	6 state mental hospitals Minnesota	chol-low.diet/ usual diet	1.1 (0.0)
UNIFACTORIAL DRUG			
Lipid Research Cl. CPPT LRC Res. Group 1984	open population, lipid clinics US	cholestyramine 24 g + diet/ placebo + diet	7.4 (6.0)
Helsinki Heart Study Frick 1987	government/industry employees, Helsinki	gemfibrozil 1,2 g + diet/ placebo + diet	5.0 (0.0)
WHO Cooperative Trial Oliver 1978	open population Prague, Budapest, Edinburgh	clofibrate 1,6 g/ olive oil placebo	5.3 (7.9)
EXCEL Bradford 1991	primary health care sources, policlinics	lovastatin 20/40 mg + diet/ placebo + diet	0.9 (0.0)
UpJohn Company Trial Dorr 1978	108 clinics US	colestipol 15 g/ placebo	2.1 (0.0)
Mc Caughan 1981	outpatient clinic Massachusetts	probucol 1000 mg/ placebo	0.9 (0.0)
Gross 1973	outpatient department New York	colestipol 5 gr/ placebo	1.3 (0.0)
MULTIFACTORIAL			
MRFIT MRFIT Res. Group 1982	government/industry employees + open population, US	chol-low. diet/ usual diet	7.0 (3.8)
Diet + Anti-Smoking Trial Hjermann 1981	open population Oslo	chol-low. diet/ usual diet	5.0 (3.5)
WHO Eur Collabor. Trial WHO Coll. 1986	80 factories Belgium, Italy, Poland, UK	chol-low. diet/ usual diet	4.8 (0.0)
Göteborg Multifact. Trial Wilhelmsen 1986	open population Göteborg	chol-low. diet (+ clofibrate/nicot. acid)/ usual diet	10.0 (1.8)
KRIS Appels 1989	open population Rotterdam	clofibrate + diet/ placebo + diet	7.8 (0.0)
Finnish Multifactorial PPT Miettinen 1985	business executives Helsinki	chol-low. diet (+ lipid-low. drug)/ usual care	5.0 (9.0)

No of patients (treatment/ control)	Inclusion/exclusion	Mean age (yrs), males (%)	Mean base-line chol (mmol/l)	Change in chol (%)*
424/422	age>55, excluded; ♀-DM-alcoholism-life limiting diseases	66, 100	6.1	-13
4541/4516	no restrictions	48, 49	5.4	-14
1907/1899	age 35-59, chol>6.7, excluded; ♀-CHD-DM-hypertension-life limiting diseases	48, 100	7.6	-9
2051/2030	age 40-55, non-HDL-chol>5.2, excl; ♀-CHD-DM	47, 100	7.0	-10
5331/5296	age 30-59, upper third of chol-distribution, excl; ♀-CHD-DM-hypertension-life lim. dis.	46, 100	6.4	-9
6582/1663	age 18-70, chol 6.2-7.8, excl; premenopause-DM-liver/kidney dis.-hypothyr.-life lim. dis.	56, 59	6.7	-24
1149/1129	age>18, chol>6.5, excluded; premenopause-lipid-low drugs-liver/kidney dis-hypothyr.	54, 48	8.0	-9
88/30	chol>6.5, excluded; multiple MI-MI within 6 mths-lipid low. drugs	50, 100	7.9	-8
23/29	>35 yrs, chol>6.5, excluded; premenopause-lipid low. drugs-liver/kidney disease	57, 29	7.7	-10
6428/6438	age 35-57, upper 15% of chol+RR, excl; ♀-CHD-DM-chol>9.0-DBP>115mmHg-lipid low.dr.-life lim. dis	46, 100	6.6	-3
604/628	age 40-49, chol 7.5-9.8, upper 25% of chol+ RR, excl; ♀-CHD-DM-SBP>150mmHg-alcoholism-life lim. dis	45, 100	8.4	-9
30,489/26,971	individual advice to upper 20% with risk of CHD, excluded; ♀	48, 100	5.6	-1
10,004/10,011	age 47-55, excluded; ♀	51, 100	6.5	-0
195/196	age 44-60, chol>6.5/DBP 95-115/gluc-intol, excluded; ♀-CHD-life lim. dis	- 100	-	-
612/610	age 40-55, chol>7.0/hypert/>10 sig/gluc-intol, excl; ♀-CHD-IDDM-renal dis.-DBP>115-SBP>200 mmHg-life lim. dis.	48, 100	7.1	-6

Secondary prevention trials

Study author, publication year	Setting	Intervention (treatment/control) (doses per day)	Mean duration (yrs) (Post follow-up)
UNIFACTORIAL DIET			
Indian Nutrition Experim. Singh '92	primary + secondary care centres, Moradabad	fruit + vegetable chol-low.diet/ chol-low. diet	2.0 (0.0)
Oslo Diet-Heart Study Leren '70	medical departments Oslo	chol-low. diet/ usual diet	5.0 (6.0)
DART Burr '89	21 hospitals in Wales UK	fat (and fish/fibre advice)/ no fat advice	2.0 (0.0)
Low Fat Diet Trial MRC (Ball) '65	medical departments London	chol-low. diet/ usual diet	3.0 (0.0)
Fish Oil Trial Reis '89	medical department Boston	fish oil 6 g/ olive oil placebo	0.6 (0.0)
Sydney Diet Heart Study Woodhill '78	medical departments Sydney	chol-low. diet/ usual diet	5.0 (0.0)
Nutritional Program Study Morrison '60	medical department Los Angeles	chol-low. diet/ usual diet	3.0 (9.0)
Soya-bean Trial MRC (Morris) '68	4 medical departments London	soya-bean oil 85 g + chol-low. diet/ usual diet	3.5 (0.0)
Corn Oil Trial Rose '65	medical departments London	corn oil/olive oil 80 g + chol-low. diet/ usual diet	1.2 (0.0)
UNIFACTORIAL DRUG			
Coronary Drug Project Canner '86	53 clinical centres US + Puerto Rico	estrogen 2.5/5 mg/thyrox. 6mg/clofibr.1.8g/niacin 3.0 g/ placebo	4.7/ 1.5/ 3.0/ 6.2/ 6.2 (8.8)
Frick 93	government/industry employees, Helsinki	gemfibrozil 1.2 g + diet/ placebo + diet	5.0 (0.0)
NHLBI Cor. Interv. Study Brensike '84	open population Washington	cholestyramine 24 g + diet/ placebo + diet	5.0 (0.0)
Effectiveness of Estrogen Stamler '63	medical department Chicago	oestrogen 10.0 mg/ placebo	4.8 (0.0)
CLAS Cashin '90	medical depart. + open population, Los Angeles	colest.30g + niacin 3-12g + diet/ placebo + diet	4.0 (0.0)
FATS Brown '90	lipid research clinic (?) Washington	colestipol 15-30g + niacin 4-6g/ colest.+ lovast. 20-40mg/ placebo	2.5 (0.0)

No of patients (treatment/ control)	Inclusion/exclusion	Mean age (yrs), males (%)	Mean base-line chol (mmol/l)	Change in chol (%)*
204/202	<2 days after AMI, excluded; diarrhoea-kidney disease-cancer	51, 90	5.9	-8
206/206	MI 1-2 yrs ago, excl; ♀-DM-CVA-kidney dis-psychiatric dis-alcoholism-life lim. dis.	56, 100	7.7	-14
1018/1015	age<70, ± 41 days after MI, excluded: ♀-DM-indications for cardiac surgery	57, 100	6.5	-4
130/134	age<65, <12 wks after first MI, excluded; ♀-DM-heart failure-hypothyroism-anticoag.	NA, 100	6.8	-6
137/67	discharge after PTCA, excl; acute PTCA-acute MI-anticoagulans-bleeding-history	59, 74	5.6	-0
221/237	age 30-59, >8 wks after MI/AP, excluded: ♀	49, 100	7.3	-4
50/50	<6 mths after MI, excluded; DM-hypertension-kidney dis-thyroid disease-xanthomatosis	61, 86	8.1	NA
199/194	age<60, <12 wks after first MI, excl; ♀-DM-DBP>110 mmHg-heart failure-anticoag.	NA, 100	7.1	-13
54/26	age<70, (recent) MI/AP, excluded; ♀-hypertension-heart failure-life limiting diseases	56, 100	6.7	-9
1101/1119/ 1083/ 1103/ 1119/2789	age 30-64, >12wks after MI, excluded; ♀-DM-AP class 3/4-anticoagulans-alcoholism-psychosis-life limiting diseases	NA, 100	6.5	-1, -2, -10, -5, -10#
311/317	age 40-55, non-HDL-chol>5.2, excluded; ♀-DM	49, 100	7.0	-9
71/72	age 21-55, angiogr.CHD, LDL upper 5%, excl; AP-heart fail.-RR↑-liver dis-life lim.d.	46, 80	7.9	-18
156/119	age < 50, >8wks after MI, excluded; ♀-heart failure	NA, 100	6.4	-3
94/94	age 40-59, CBAG >3 mths ago, chol 4.9-9.1, excl; ♀-DM-RR↑-thyroid/renal dis-heart fail.	54, 100	6.3	-22
48/46/52	age < 62, angiographic CHD, high apolip.B, fam.history of CHD, excl; ♀-DM-hypert.-liver/thyroid/kidney dis.-cancer	46, 100	7.0	-19, -29

continued

	Intervention (treatment/control) (doses per day)	Mean duration (yrs) (Post follow-up)
department n-Trent, UK	clofibrate 1.0-2.0 gr/ corn oil placebo	± 6 (0.0)
. department ›lm	clofibrate 2 g + nicotinic acid 3 g/ placebo	3.6 (0.0)
/cardiologists stle-upon-Tyne UK	clofibrate 1.5-2 g/ placebo	3.5 (0.0)
cal wards rgh	oestrogen 2.5-3.0 mg/ placebo	4.5 (0.0)
l department Italy	pravastatin 20 mg + diet/ diet	1.0 (0.0)
al department /lvania	lovastatin 20-40 mg + usual drugs/ usual drugs	2.0 (0.0)
spitals nd	clofibrate 1.6-2 g/ olive oil placebo	3.4 (0.0)
\ hospitals	estrogen 1.25mg/thyroxine 4 g/nicot.acid 4g/ estr. + thyr/estr.+nic.acid/ plac.	3.2 (0.0)
:al department ›n	cholestyramine 16 g + diet/ diet/ usual care	3.3 (0.0)
betic clinics ›l UK	clofibrate 1600 mg/ corn oil placebo	1.0 (0.0)
clinic Francisco	niacin >1.5g/ colestipol 15-30g/ lovast 40-60mg + diet/ diet (+ colest.15g)	2.0 (0.0)
spitals Angeles	oestradiol/ placebo	3.0 (0.0)
nesota, Arkansas, Califor- Philadelphia hospitals	partial ileal bypass + diet/ usual care + diet	9.7 (0.0)
ıedical departments land	chol-low. diet/ usual care	2.5 (0.0)
dical department idelberg, Germany	chol-low. diet/ usual care	0.9 (0.0)
:dical department lifornia	vegetarian chol-low. diet/ usual care	0.9 (0.0)

No of patients (treatment/ control)	Inclusion/exclusion	Mean age (yrs), males (%)	Mean base-line chol (mmol/l)	Change in chol (%)*
47/48##	CVD >4 mths ago, chol>6.5, no restrictions	NA, 68	7.5	-8
279/276	age<70, discharge after MI, excl; DM-RR↑-heart failure-kidney/liver dis.-cancer	60, 80	6.4	-13
244/253	age<65, >6wks after MI, excl; chol<10.5-DM-heart failure-RR↑-kidney dis-life lim dis	53, 81	6.5	-12
50/50	age 35-64, 3-4 mths after MI, excl; ♀-DM-RR↑-chol>10.5-heart failure-thyroid disease	-, 100	6.1	-13
48/46	age<70, chol>5.2, <1 yr after MI/AP/CVA/-TIA, excl; secondary hyperlipidaemia	61, NA	6.9	-20
79/78	just performed successful PTCA, excl; neces-sity of bypass-lovastatin use-liver dis.	60, 71	5.4	-12
264/273	age 40-69, 2-4 mths after MI, excl; DM-heart failure	53, 79	7.0	-6
141/74/77/ 67/68/143	age 25-75, < 1 yr after MI, excl; life lim dis	51, 100	6.2	-3, -5, -15, -7, -13#
30/30/30	age<66, chol>6.0, angiogr CHD, excl; MI<8 wks-DM-RR↑-heart failure-life lim d.	51, 100	7.2	-23, -12
30/33	diabetic retinopathy, no restrictions	NA, 57	NA	NA
48/49	19-72 yrs, het.FH, angiogr.CHD, excl; mul-tiple MI-CABG-second.hyperlip.-syst.dis.	41, 43	9.6	-22
285/147	at discharge after MI, excl; CVA-kidney/liver disease-life lim dis.	NA, NA	NA	NA
421/417	age 30-64, MI<6-60 mths, chol>5.7, excl; DM-RR↑-sec.hyperlip.-heart fail-life lim.dis.	51, 91	6.5	-22
188/187	age<65, at discharge after MI, no restrictions	54, 80	6.0	-13
56/57	stable AP, excl; unstable AP-very low cho-lesterol-DM-heart failure	54, 100	6.1	-10
28/20	age 35-75, >6 wks after MI, excl; anti-coa-gulans-heart failure-life lim. disease	58, 86	6.1	-19

Appendix 4

Results of quality assessment of the trials included in chapter 7

Secondary prevention trials

trials criteria	A1	2	3	4	5	6	7	B1	2	3	4	5	6	7	C1	2	3	4	5	6	7	8	9	Sum
diet																								
Singh 92	8	5		3		8					5			5		3	2	3		2	3		7	**54**
Leren 70	8		-8	3		8								5		3	2	3	3	12	3		7	**49**
Burr 89	8	5									5				7	3	2	3		2	3	2	7	**47**
Ball 65		5		3							5			5		3	2	3		7			7	**40**
Reis 89		5	-8	3	-5	8		6		5	5	2	2	5		3	2	3	3	-5	3	2		**39**
Woodhill 78		5														3	2	3		12	3	2	7	**37**
Morrison 60		5				8	-5									3	2			12			7	**32**
Morris 68		5	-8	3	-5	8					5			5		3	2	3		7				**28**
Rose 65		5	-8	3	-5									5		3	2	3		2				**10**
drugs																								
Canner 86	8	5				8		6		5	5	2		5	7	3	2	3	3	12	3	2	7	**86**
Frick 93	8	5	-8			8		6		5	5	2	2	5		3	2	3	3	12	3		7	**71**
Brensike 84	8		-8		-5			6		5	5	2	2	5		3	2	3	3	12	3	2	7	**55**
Stamler 63	8	5	-8			8				5		2				3		3	3	12			7	**48**
Cashin 90	8	5	-8			8			1		5	2				3	2	3	3	7	3			**42**
Brown 90			-8	3		8		6			5	2	2	5		3	2	3	3	2	3	2		**41**
Acheson 72	8	5	-8	3	-5						5	2				3	2			12	3		7	**37**
Carlson 72		5	-8	3		8										3	2	3		7	3		7	**33**

Newcastle 71		5	-8	3	-5			6			5	2	2	5		3	2	3	3	7				**33**
Oliver 61		5	-8	3								2				3	2	3		12			7	**29**
Bellandi 93		5				8								5		3							7	**28**
Sahni 91				3										5		3	2	3	3				7	**26**
Scottish Soc 71			-8	3	-5			6			5	2	2	5		3	2	3		7				**25**
Schoch 68	5				-5		-5					2	2			3		3	3	7			7	**22**
Watts 92		5	-8	3	-5											3	2	3		7	3	2	7	**22**
Harrold 69			-8	3	-5		-5	6	5	5	2	2				3	2	3	3	2				**18**
Kane 90	8	5	-8	3	-5														3	2				**18**
Marmorston 62		5			-5		-5					2				3	2	3		7				**12**
surgical																									
Buchwald 90	5	5		3		8								5		3	2	3	3	12	3	2	7	**61**
multifactorial																									
Kallio 79		5		3	-5	8								5		3				2	3		7	**31**
Schuler 92		5	-8	3	-5						5			5		3	2	3		2	3			**18**
Ornish 90		5	-8	3	-5		-5				5			5		3	2	3		2	3			**13**

Primary prevention trials

trials criteria	A1	2	3	4	5	6	7	B1	2	3	4	5	6	7	C1	2	3	4	5	6	7	8	9	Sum
diet																								
Dayton 69		5	-8	3		8		6		5	5	2	2	5		3	2	3		2	3		7	**53**
Frantz 89					-5			6		5	5	2			15	3	2	3					7	**43**
drugs																								
LRC 84	8	5				8		6	1	5	5	2	2	5		3	2	3	3	7	3	2	7	**77**
Frick 87	8	5	-8			8		6		5	5	2	2	5	7	3	2	3	3	2	3	2	7	**70**
Oliver 78		5	-8	3	-5			6		5	5	2	2	5	15	3	2	3	3	2	3	2	7	**60**
Bradford 91		5	-8	3	-5	8		6		5	5	2	2	5		3	2	3	3	-5	3		7	**44**
Dorr 78	8	5	-8			8				5	5	2				3			3		3		7	**41**
McCaughan 81			-8	3	-5			6		5	5	2				3	2	3	3		3		7	**29**
Gross 73			-8	3	-5		-5	6		5	5	2	2				3		3					**5**
multifactorial																								
MRFIT 82	8	5				8					5			5	15	3	2	3		7	3	2	7	**73**
Hjermann 81	8	5				8					5			5		3	2	3		7	3	2	7	**58**
WHO 86	8	5				8								5	15	3				2	3	2	7	**58**
Wilhelmsen 86						8					5				15	3				12	3	2	7	**55**
Appels 89	8	5	-8	3	-5			6	1	5		2	2	5		3	2	3		7	3	2	7	**51**
Miettinen 85		5	-8								5			5		3	2			2	3	2	7	**26**

Summary

The subject of this thesis is the national guidelines on cholesterol developed by the Dutch College of General Practitioners (DCGP). The cholesterol guidelines, which are extensively described in appendix 1, were published in 1991 and form part of a long series of DCGP practice guidelines, with the first guideline published in 1989. The initiative for the research project underlying this thesis was taken by the Centre for Quality of Care Research in collaboration with the DCGP. The research project started in March 1991 and ended in June 1994, and was financially supported by the Netherlands Heart Foundation. At the start it was decided to run two parallel projects; one focusing at the feasibility of the cholesterol guidelines, which might lead to recommendations for implementation, and the other focusing on the scientific base of the guidelines, which might lead to recommendations for updating the guidelines. The state of the art at the start of the project is described in chapter 1, together with the research questions underlying this thesis. The investigation of the usual care given by Dutch general practitioners (GPs) in relation to the DCGP cholesterol guidelines is described in chapters 2 to 4, in which three different data bases were analysed. The feasibility of the cholesterol guidelines is examined in chapters 5 and 6, describing an implementation study in the format of a randomised controlled trial on a systematically developed programme for improvement (appendix 2), and an analysis of the barriers for adherence to the guidelines. An attempt to explore the scientific base of the guidelines at meta level is described in chapters 7 and 8. Both randomised controlled trials on the effect of cholesterol-lowering interventions and economic evaluation studies on the cost-effectiveness of cholesterol lowering are reviewed systematically. In chapter 9 the results of the different chapters are discussed, integrated and interpreted, and recommendations for both implementing and updating the guidelines as well as for further research are made.

Chapter 1 discusses the relevance of national guidelines on cholesterol management in general practice and the rationale for evaluation of these practice guidelines. The cholesterol guidelines were developed through a consensus procedure and based as much as possible on the scientific data published in the literature. The evidence that was available during the development of the guidelines is described in the first part of the introduction chapter, summarising the state of the art at the start of this research project. The conclusions from this available evidence are reported together with the description of the guidelines themselves. The second part of this chapter describes a research model for evaluation of practice guidelines. The research model is divided in two main objectives: the evaluation of the feasibility of the guidelines, and the evaluation of its scientific validity. Finally, the translation of the research model for evaluation of practice guidelines into the research questions as well as the structure of this book are outlined.

The key questions are:
Are the guidelines feasible and applicable in practice?

1.1 What is the usual care in Dutch general practices regarding screening and management of hypercholesterolaemia like? Does discrepancy exist between current practice and the DCGP standard on Cholesterol?
1.2 If discrepancy exists between current practice and the guidelines, what are the barriers for adherence to the guideline? Which strategies can be developed to optimise the implementation of the guidelines?
1.3 Are the guidelines used after application of intensive implementation strategies?

What is the evidence base of the guidelines?

2.1 What is the scientific evidence on the effectiveness of cholesterol lowering on coronary heart disease (CHD) morbidity, non-CHD morbidity, CHD mortality and total mortality? Is the evidence generalisable to the general practice setting?
2.2 What is the present state of the scientific evidence on the cost-effectiveness of different cholesterol screening strategies in general practice?

Investigation of usual care
Data of the 'Dutch National Survey of General Practice' (1987-88, with 161 participating GPs), in which GPs were involved in extensive consultation registration, were used. Patients were included for analysis if serum cholesterol, or the ICPC-code lipid metabolism disorder, or cholesterol-lowering treatment was registered (**chapter 2**). A second data base was created by retrospective audit of 3577 adult patients' records, systematically sampled from 20 general practices during the years 1990-92. With criteria set by the national guidelines, the proportion of patients per practice (a) for whom cholesterol testing would be considered justified, and (b) for whom cholesterol testing would be considered unjustified, and the proportion of patients within each of these groups who had had a cholesterol measurement recorded are described (**chapter 3**). Analysis of total cholesterol and lipid fraction tests at the Maastricht Diagnostic Centre, which served all 85 GPs in the region, over the years 1984-1992 formed the third data source. The frequency of cholesterol and lipid fraction testing in 'new patients' (patients presenting for cholesterol testing for the first time) were indicators for adherence to the guidelines on the diagnostic procedure. Data on new patients were available for the years 1989-1992 (**chapter 4**).

Managing hypercholesterolaemia was not a clear-cut task for Dutch GPs in the years before the guidelines were published (chapter 2). Especially the variation in screening policy among GPs was high. Other main discrepancies between daily practice and the guidelines concerned the repetition of measurements to diagnose hypercholesterolaemia, and the attention given to diet advice. Cholesterol-lowering drugs (the HMG coA inhibitors were not on the market yet) were prescribed to 25% of the patients with

hypercholesterolaemia.

The proportion of patients tested that did not fulfil the age criteria for testing according to the guidelines was stable throughout the years: one-fifth of the patients tested were older than 65 (25.4% women and 17.4% men) before publication of the guidelines (chapter 2); this was 17% (women over 65 twice as likely to be tested than men over 65) around the publication of the guidelines (chapter 3); the trend analysis showed 13.5% of male and 23.0% of female patients to be older than 65 years over the years (chapter 4).

Targeting cholesterol testing to those individuals with an increased risk profile for coronary heart disease (CHD) was problematic (chapter 3). Nearly 13% of the patients in a general practice were recorded as having a positive cardiovascular risk profile, according the definition in the guidelines. Cholesterol tests were performed on average in nearly 12% of the adult patients. The major problem was failure to test those likely to benefit. Less than one-third (31%) of the patients with an indication for testing were actually tested.

A rising trend in cholesterol test ordering by GPs was seen over the years 1984-1992 (chapter 4). The amount of testing nearly doubled during that time (net increase of 173%). There is considerable and persistant inter-doctor variation in test-ordering, despite the stabilisation in the amount of testing in 1990 and the publication of the guidelines in 1991. Repetition of cholesterol testing to diagnose hypercholesterolaemia was performed in less than 0.5% of the new patients. HDL and/or triglyceride testing is not indicated according the guidelines in new patients. Nevertheless, although a slight decreasing trend was seen, 31% of the new patients were tested on lipid fractions in 1992.

It was concluded from these three data sources that GPs do not seem to adhere to the guidelines, and that despite a rising trend in cholesterol testing considerable and persistant inter-doctor variation exists. The main problems were seen in the adherence to age criteria for screening, as well as the adherence to indications for screening related to the patient's risk profile, in the repetition of testing necessary to diagnose hypercholesterolaemia, and in the doctor's and patient's compliance to diet therapy.

Feasibility of the guidelines

The considerable discrepancy between the guidelines on cholesterol management and current behaviour of GPs, reported in chapters 2-4, led therefore to the development of an educational programme for GPs regarding implementation of these guidelines, using a systematic stepwise approach (appendix 2). The educational programme had to be focussed on the barriers to adherence to the guidelines. Several barriers to adherence to the guidelines were investigated by questioning two groups of GPs, one representative for Dutch GPs and one representing GPs with special interest in the topic. These barriers and needs were translated into educational objectives and optimal learning conditions. Strategies and methods were developed based on the barriers to change, and incorporated in a programme for improvement designed to meet these educational objectives. Barriers most often mentioned were lack of time and/or motivation for preventive activities in general, and for repeat testing for diagnosis and diet therapy in particular. Other barriers

frequently mentioned were lack of skills to deal with demanding patients (patients actively asking for cholesterol testing), and the complexity of the management algorithm. An intensive 5-month programme was developed consisting of an educational group session, several supportive educational materials, continuous registration of 'cholesterol consultations' by the GPs (reminders), feedback on performance, and face-to-face instruction during two sessions on location.

The impact of the programme for improvement on both knowledge and attitude (**chapter 6**) and actual performance (**chapter 5**) was tested in a randomised controlled trial. The guidelines were disseminated to all 32 participating GPs in 20 practices, and implemented in half of these practices with the programme for improvement. The trial was conducted with a follow-up measurement one year after baseline and a 5-month intervention period in between. Comparability of the two groups was assured by means of stratified randomisation at practice level. Instruments for measurement of (barriers to) change were a knowledge test, an attitude questionnaire, chart audit, consultation registration, and an interview. The GPs increased their knowledge of the guidelines immediately after the educational group session, but this effect had disappeared completely at follow-up measurement nine months later. Although the level of agreement with the guidelines was rather high, the GPs' opinion of the feasibility of the guidelines remained low throughout the trial. The quantity of cholesterol testing increased, but this was not accompanied by an increase in the quality of cholesterol testing. The targeting of cholesterol testing to those with positive risk profiles (the selective case finding) did not improve following intervention. Performance of repeat testing necessary to diagnose hypercholesterolaemia even deteriorated, and the application of diet therapy also decreased following intervention.

The participating GPs were questioned about barriers to change at the end of the intervention period (chapter 6). Professional-related barriers in the area of knowledge or attitude were: a lack of priority for prevention ("I just don't think of case finding"), the time-consuming nature of preventive procedures (without reimbursement), the trouble both for the GP and the patient of repeating the cholesterol test three times, hesitation to intervene in a patient's lifestyle, and doubt about the cost-effectiveness of cholesterol intervention. Professional-related barriers in the area of skills were difficulties to change practice routines, and feeling of incompetence in guiding patients for diet therapy. Other barriers were not directly related to the professional: the complexity of the guideline algorithm, practical problems in monitoring the patient's risk profile, difficulties to change both practice organisation and lifestyle for the patient ("diet therapy is frustrating, both for the patient and the GP"), patients actively demanding cholesterol testing ("I'm a doctor, not a negotiator"), interference by cardiologists'/internists' cholesterol management which deviates from the guidelines, and lack of cooperation with these specialists.

Evidence base of the guidelines

The efficacy of cholesterol-lowering interventions was assessed in a systematic review of the literature (**chapter 7**). The results of 46 randomised controlled trials of cholesterol-

lowering interventions, published before 1994, were included in a qualitative and quantitative meta-analysis. Much attention was given to the quality assessment of the trials. Three independent experts in the field of CHD and/ or methodology of clinical trials independently assessed the quality in a stadardised way. Moreover, the judges were blinded for information that might have biased their judgements on methodological quality, e.g. the journal in which the trial was published, or the results of the trial. These trials included 132,296 patients with CHD and 30,515 patients without CHD. Cholesterol lowering had a favourable effect on non-fatal myocardial infarction for men without CHD (odds ratio 0.86 (CI 0.75-0.99)), whereas the pooled effect for men with CHD was non-significant and heterogeneous. The pooled odds ratio on CHD deaths, both men and women included, was of borderline significance and heterogeneous (0.94 (CI 0.89-1.00)), and comparable for people with or without CHD. The pooled odds ratio on total deaths, for the better than average studies, was 1.02 (CI 0.95-1.08) for people without CHD, and 0.93 (CI 0.85-1.02) for patients with CHD.

After the inclusion of trials for chapter 7 was closed, the results of at least 19 new cholesterol-lowering intervention trials were published, which focus on the effectiveness of the HMG-coA reductase inhibitors (**chapter 7 update**). Five new trials concerned primarily clinical outcomes and 14 new trials concerned primarily angiographical outcomes. The effect of cholesterol lowering is established in patients with CHD. The recent finding that cholesterol lowering reduced total mortality in CHD patients is of great importance in this matter. The evidence is convincing for the subgroup of middle-aged white men, but the transferability of the results to real-life patients was the critical, unanswered question. At the same time there is far less information and more uncertainty on the interpretation of the smaller benefits of cholesterol lowering in persons without CHD. Screening on serum cholesterol levels is most likely to be useful when done in populations at high short-term risk for dying of CHD, such as survivors of myocardial infarction and middle-aged men with multiple cardiac risk factors.

The cost-effectiveness of cholesterol-lowering interventions was appraised in another systematic review of the literature (**chapter 8**). The results of 37 economic evaluations published before 1997 were described, with special interest in the representativeness of the study populations on which cost-assessments were based (was efficacy corrected for community-effectiveness?) and the type of costs that were taken into account (eg. intangible costs). Costs of screening to target cholesterol-lowering interventions to persons with hypercholesterolaemia were considered in seven studies only. Adjustments of the efficacy of the interventions for community effectiveness were rarely described and intangible costs were rarely taken into account. The literature on unfavourable side-effects of cholesterol screening or decrease in effectiveness in the community is discussed, with problems such as misclassification of persons with respect to the serum cholesterol level due to measurement error, labelling of persons as hypercholesterolaemic patients, or the loss in quality of life due to diet therapy. Cost-effectiveness ratios ranged from $0 to more than $1 million per year of life saved and were highly dependent on gender and risk profile of the patient,

on cost of the drug, and on the types of costs that were included in the calculations. Despite the large variation in outcomes, there was a constant tendency towards a more favourable cost-effectiveness ratio for intervening in persons with CHD compared to persons without CHD and for men compared to women.

In **chapter 9** we have summarised the main results and related the conclusions of the earlier chapters under the topics 'investigation of usual care', 'feasibility of the guidelines' and the 'evidence base of the guidelines'. Some methodological considerations that had not received attention earlier are discussed. The usefulness of the research model as it was presented in chapter 1 is considered, and the fact that the predictive value of total serum cholesterol in relation to CHD is still under discussion. Possible methodological flaws of the RCT on the programme of improvement are discussed, and the strengths and weaknesses of the literature reviews. We tried to integrate and interpret the results of this thesis. Many possible explanations for the low feasibility of the cholesterol guidelines are discussed. The transferability of the new evidence on efficacy of cholesterol lowering to real-life general practice patients remained the critical, unanswered question. Finally, the results are translated into recommendations for updating the guidelines and for strategies for implementation. The indications for cholesterol testing can be restricted. Restriction seems rational to patients with symptoms of coronary heart disease and patients with symptoms of familial hypercholesterolaemia. Considering the unfavourable cost-effectiveness ratio and the low feasibility of selective case finding based on the coronary risk profile, caution is needed in screening persons without CHD. The usefulness of risk tables to target individuals with multiple cardiac risk factors (e.g. the Sheffield risk tables) needs further clarification. An integrated standard for prevention of (recurrent) coronary heart disease is needed from a scientific point of view, and will probably lead to higher adherence than the separate hypertension and cholesterol guidelines which now co-exist. In addition, we give some recommendations for further research in this field.

Samenvatting

Dit proefschrift gaat over de landelijke richtlijnen voor cholesterol diagnostiek en therapie van het Nederlands Huisartsen Genootschap, de NHG-standaard Cholesterol. De standaard richtlijnen werden gepubliceerd in 1991. Het initiatief voor het aan dit proefschrift onderhavige onderzoeks-project werd genomen door de Werkgroep Onderzoek Kwaliteit (WOK Nijmegen/Maastricht) in samenwerking met het NHG. Het project liep van maart 1991 tot juni 1994, en werd gefinancierd door de Nederlandse Hart Stichting. Bij aanvang werd besloten twee parallel-projecten uit te voeren; één gericht op de haalbaarheid van de cholesterol-richtlijnen in de dagelijkse praktijk, leidend tot aanbevelingen voor implementatie, en de ander gericht op de wetenschappelije onderbouwing van de richtlijnen, leidend tot aanbevelingen voor actualisering van de richtlijnen. De heersende kennis en opinie bij de start van het project staan samengevat in hoofdstuk 1, samen met de vraagstellingen van dit proefschrift. In hoofdstuk 2 tot en met 4 wordt de huidige zorg door Nederlandse huisartsen vergeleken met de optimale zorg volgens de NHG-standaard richtlijnen. De haalbaarheid van de cholesterol-richtlijnen wordt aan de kaak gesteld in hoofdstuk 5 en 6. Hierin wordt verslag gedaan van het effect van een programma voor kwaliteitsverbetering gericht op het werken volgens de standaard, en van een analyse van de knelpunten voor het werken volgens de richtlijnen. In hoofdstuk 7 en 8 wordt de wetenschappelijke basis van de cholesterol-richtlijnen geëxploreerd. Er wordt een systematisch overzicht gegeven van 'randomised controlled trials' (RCTs) naar het effect van cholesterol-verlaging, en van economische evaluaties naar de kosten-effectiviteit van cholesterol-verlaging. In hoofdstuk 9 worden de resultaten van de diverse hoofdstukken beschouwd en geïntegreerd, en worden aanbevelingen gedaan voor zowel implementatie als actualisatie van de richtlijnen.

De relevantie van de cholesterol-richtlijnen voor de huisartsgeneeskunde wordt beschreven in **Hoofdstuk 1**. De richtlijnen werden ontwikkeld middels een consensus-procedure waarbij de wetenschappelijke literatuur het uitgangspunt vormde. De wetenschappelijke basis die beschikbaar was ten tijde van het tot stand komen van de richtlijnen wordt samengevat in het eerste deel van hoofdstuk 1. Vervolgens worden de conclusies die hieruit voortvloeiden beschreven, samen met de kern-richtlijnen (tabel 3, pagina 7). In het tweede deel van dit hoofdstuk wordt een onderzoeksmodel voor evaluatie van praktijk-richtlijnen gepresenteerd (pagina 8). Het onderzoeksmodel visualiseert de twee hoofdbestanddelen van dit project: de evaluatie van de haalbaarheid, en de evaluatie van de wetenschappelijke validiteit van de richtlijnen. Tenslotte wordt het onderzoeksmodel vertaald in de vraagstellingen, en de indeling van het proefschrift toegelicht.

De vraagstellingen luiden:

Zijn de richtlijnen haalbaar en toepasbaar in de dagelijkse praktijk?

1.1 Wat doen Nederlandse huisartsen aan cholesterol-diagnostiek en -therapie? Bestaat er discrepantie tussen de huidige zorg en de optimale zorg volgens de richtlijnen?

1.2 Als er discrepantie bestaat, wat zijn dan de knelpunten die het werken volgens de richtlijnen in de weg staan? Welke strategieën kunnen worden ontwikkeld om de implementatie van de richtlijnen te bevorderen?

1.3 Worden de richtlijnen beter toegepast na intensieve implementatie?

Hoe is de wetenschappelijke onderbouwing van de richtlijnen?

2.1 Wat zijn de wetenschappelijke inzichten over het effect van cholesterol-verlaging op morbiditeit door coronaire hartziekte (CHZ), op sterfte door CHZ, en op totale sterfte? In hoeverre is de beschikbare kennis generaliseerbaar naar de huisartsgeneeskundige setting?

2.2 Wat zijn de wetenschappelijke inzichten over de kosten-effectiviteit van screenings-strategieën ten aanzien van hypercholesterolaemie in de huisartsgeneeskunde?

Inventarisatie van de huidige zorg

In **hoofdstuk 2** worden data gerapporteerd van de 'Nationale Studie' van het NIVEL (1987-88), waarin 161 huisartsen drie maanden lang alle patiënt-contacten registreerden. Alle consulten waarbij een cholesterolwaarde, of de ICPC-code vetstofwisselingsstoornis, of cholesterol-verlagende therapie werd geregistreerd, werden geanalyseerd. Een tweede gegevensbron werd gecreeërd door patiëntkaart-analyse van 3577 volwassen patiënten over de jaren 1990-1992, welke steekproefgewijs werden geselecteerd uit de registratiesystemen van 20 huisartspraktijken (**hoofdstuk 3**). Door toepassing van de criteria voor screening wordt de proportie patiënten per praktijk beschreven (a) voor wie cholesterolbepaling terecht, en (b) voor wie cholesterolbepaling onterecht zou zijn, alsmede de proportie patiënten binnen ieder van deze groepen voor wie een cholesterolbepaling daadwerkelijk werd genoteerd. De lipiden aanvraaggevens over de jaren 1984-1992 van het Maastrichtse Diagnostisch Coördinerend Centrum, dat alle 85 huisartsen in de regio bediend, vormde een derde gegevensbron (**hoofdstuk 4**). De frequentie van cholesterol en lipiden-fractie bepalingen vormden indicatoren voor het werken volgens de richtlijn voor diagnostiek.

Een duidelijke taakopvatting wat betreft het beleid bij hypercholesterolaemie ontbrak in de huisartsgeneeskunde in de jaren voordat de richtlijnen werden gepubliceerd (hoofdstuk 2). Er bestond grote variatie in het screeningsbeleid tussen huisartsen onderling. Andere belangrijke discrepanties tussen de dagelijkse praktijk en de richtlijnen betroffen het herhaald bepalen van het serumcholesterol ten behoeve van de diagnose hypercholesterolaemie, en de aandacht die werd gegeven aan dieet-advisering. Cholesterol-verlagende medicatie (de HMG coA synthese remmers waren nog niet op de markt) werd voorgeschreven aan 25% van de patiënten met hypercholesterolaemie.

Het aandeel patiënten dat niet voldeed aan de leeftijds-criteria voor screening maar

desondanks toch werd getest op serumcholesterol was vergelijkbaar door de jaren heen: een-vijfde van de patiënten die op serumcholesterol waren gescreend waren ouder dan 65 jaar (25.4% van de vrouwen en 17.4% van de mannen) vóór de publicatie van de richtlijnen (hoofdstuk 2); dit was 17% (waarbij vrouwen boven de 65 twee maal zo vaak werden getest dan 65^{+} mannen) rond de publicatie van de richtlijnen (hoofdstuk 3); en uit de trendanalyse over de jaren 1984-1992 bleek dat gemiddeld 23.0% van de vrouwen en 13.5% van de mannen ouder waren dan 65 jaar (hoofdstuk 4).

Het beperken van cholesterolscreening tot de groep individuen met een verhoogd risicoprofiel voor coronaire hartziekte vormde een probleem voor de huisarts (hoofdstuk 3). Bijna 13% van de patiënten in een huisartspraktijk hebben volgens het registratiesysteem een verhoogd cardiovasculair risicoprofiel, althans volgens de criteria in de NHG-standaard. Het serumcholesterol werd bepaald bij bijna 12% van de patiënten. Echter, niet altijd werden diegenen getest die het meest baat hebben bij cholesterolscreening. Minder dan een-derde (31%) van de patiënten met een belast risicoprofiel, en dus met een indicatie voor cholesterolscreening, werden daadwerkelijk getest.

Het aantal cholesterolbepalingen door huisartsen verdubbelde bijna gedurende de jaren 1984-1992, met een netto stijging van 173% (hoofdstuk 4). De inter-dokter variatie in testgedrag is aanhoudend groot, ondanks een stabilisatie in het aantal bepalingen in 1990 en de publicatie van de standaard-richtlijnen in 1991. Het op de juiste wijze herhaald bepalen van cholesterol ten behoeve van de diagnose hypercholesterolaemie werd in minder dan 0.5% van de patiënten toegepast. HDL of triglyceride testen zijn niet geïndiceerd volgens de NHG-standaard bij patiënten die voor het eerst een cholesterolbepaling ondergaan. Desondanks werd, ook al bestond er een licht dalende trend, bij 31% van deze patiënten getest op lipiden-fracties in 1992.

Uit deze gegevensbronnen wordt geconcludeerd dat de inter-dokter variatie aanhoudend hoog is ondanks de toename in cholesterolscreening. De cholesterol richtlijnen lijken nauwelijks doorgedrongen in de huisartsgeneeskunde. De belangrijkste knelpunten werden gezien in het hanteren van de leeftijds-criteria voor screening, in het hanteren van het risicoprofiel van de patiënt als indicatie voor screening, in het herhaald bepalen van serumcholesterol ten behoeve van de diagnose hypercholesterolaemie, en in de compliantie van zowel de huisarts als de patiënt aan dieet-therapie.

Haalbaarheid van de richtlijnen

De discrepantie tussen de huidige zorg door huisartsen en de optimale zorg volgens de richtlijnen (hoofdstuk 2-4) vormde de aanzet voor het ontwikkelen van een implementatie programma voor huisartsen, waarbij een systematische en stapsgewijze benadering werd gevolgd (appendix 2). Het programma voor kwaliteitsverbetering diende gericht te zijn op de knelpunten voor het werken volgens de richtlijnen. Diverse knelpunten werden geïnventariseerd door twee groepen huisartsen te ondervragen. Enerzijds werd een steekproef van huisartsen uit het NHG-ledenbestand geënquêteerd, anderzijds werden huisartsen met speciale interesse voor het onderwerp actief geselecteerd voor een enquête. De knelpunten

werden vertaald naar educatieve doelen en optimale leercondities. Vervolgens werden implementatie-strategieën ontwikkeld gericht op de barrières voor verandering, en ingepast in een samenhangend programma voor kwaliteitsverbetering. De meest genoemde knelpunten waren gebrek aan tijd en/of motivatie voor preventieve activiteiten in het algemeen, en voor herhaald bepalen ten behoeve van de diagnose en dieet therapie in het bijzonder. Andere vaak genoemde knelpunten betroffen gebrek aan vaardigheden in het omgaan met eisende patiënten (patiënten die actief vragen om een cholesterolbepaling), en de complexiteit van het stroomdiagram voor behandeling van hypercholesterolaemie. Het programma voor kwaliteitsverbetering duurde vijf maanden en bestond uit een educatieve groepsbijeenkomst, ondersteunende materialen, continue registratie van 'cholesterol consulten' door de huisarts (reminders), feedback op het handelen, en face-to-face instructies gedurende twee sessies op locatie.

De impact van het implementatie-programma op kennis en attitude (**hoofdstuk 6**) en op het handelen (**hoofdstuk 5**) werd geëvalueerd middels een gecontroleerd experiment. De richtlijnen werden verspreid onder de 32 participerende huisartsen uit 20 praktijken, en intensief geïmplementeerd in de helft van deze praktijken door middel van het programma voor kwaliteitsverbetering. Na een voormeting volgde de interventieperiode van vijf maanden, en tenslotte een nameting een jaar na de voormeting. Vergelijkbaarheid van de twee groepen werd nagestreefd door gestratificeerde randomisatie op praktijk-niveau. De (knelpunten voor) veranderingen werden gemeten met een kennistoets, een attitude vragenlijst, een interview, patiëntkaart-analyse, en consult-registratie. De huisartsen verbeterden hun kennis van de richtlijnen onmiddellijk na de educatieve groepsbijeenkomst. Deze verbetering was echter verdwenen tijdens de nameting. De mening van de huisartsen over de inhoud van de richtlijnen was redelijk positief. Daarentegen bleef de mening over de haalbaarheid van de richtlijnen kritisch gedurende het hele experiment. Cholesterol-screening nam kwantitatief gezien toe, wat echter niet gepaard ging met een verbetering in de kwaliteit ervan. Het beperken van cholesterol-screening tot diegenen met een belast risicoprofiel (selectieve case finding) verbeterde niet na afloop van de interventie. Het herhaald bepalen van serumcholesterol ten behoeve van de diagnose hypercholesterolaemie verslechterde zelfs, evenals het toepassen van dieet-therapie.

De deelnemende huisartsen werden na afloop van de interventie gericht ondervraagd over de knelpunten en barrières voor verandering die zij hadden ervaren (hoofdstuk 6). Knelpunten op het vlak van kennis of attitude waren: twijfel over de kosten-effectiviteit van cholesterol-screening, het tijd-verslindende karakter van preventie (terwijl vergoeding ontbreekt), de last voor patiënt en huisarts van het tot drie keer toe herhalen van de cholesterolbepaling, aarzeling om te interveniëren in de leefstijl van de patiënt ("ik wil geen dominee zijn"), en gebrek aan prioritering van preventie ("ik denk gewoon niet aan case finding"). Er werden ook knelpunten op het vlak van vaardigheden genoemd: het moeizaam veranderen van dagelijkse routines, een gevoel van incompetentie in het begeleiden van patiënten bij dieet-therapie. Sommige knelpunten waren niet direct gerelateerd aan de huisarts: de complexiteit van het stroomdiagram voor behandeling, praktische

problemen in het monitoren van het risicoprofiel, verandering in praktijkorganisatie is moeizaam te bewerkstelligen, evenals leefstijlverandering door de patiënt ("dieet therapie is frustrerend, voor patiënt én huisarts"), patiënten verzoeken actief om cholesterol screening ("ik ben dokter, geen onderhandelaar"), confrontatie met afwijkend cholesterolbeleid van cardiologen of internisten, en gebrek aan samenwerking met deze specialisten.

Wetenschappelijke basis van de richtlijnen

De effectiviteit van cholesterolverlagende interventies werd nagegaan middels een systematisch literatuur-review (**hoofdstuk 7**). De resultaten van 46 RCTs van cholesterolverlagende interventies, gepubliceerd vóór 1994, werden geïncludeerd in een kwalitatieve en kwantitatieve meta-analyse. Er werd veel aandacht gegeven aan de methodologische kwaliteit van de trials. De kwaliteit werd op gestandaardiseerde wijze beoordeeld door drie experts op het terrein van coronaire hartziekten en/of methodologie van klinische trials. De beoordelaars waren blind voor informatie die hen zou kunnen bevooroordelen, bijvoorbeeld het tijdschrift waarin de trial was gepubliceerd, of de resultaten van de trial. In totaal werden in de trials 132.296 patiënten met en 30.515 patiënten zonder coronaire hartziekte (CHZ) geïncludeerd. Cholesterolverlaging had een gunstig effect op niet-fatale myocard infarcten (MI) voor mannen zonder CHZ (odds ratio 0.86 (BI 0.75-0.99)), terwijl het gepoolde effect voor mannen mét CHZ niet-significant en heterogeen was. De gepoolde odds ratio op CHZ sterfte, voor mannen en vrouwen samen, was borderline significant en heterogeen (odds ratio 0.94 (BI 0.89-1.00)), en vergelijkbaar voor personen met of zonder CHZ. De gepoolde odds ratio voor totale sterfte, voor de kwalitatief betere studies, was 1.02 (BI 0.95-1.08) voor personen zonder CHZ, en 0.93 (BI 0.85-1.02) voor patiënten met CHZ.

Nadat het includeren van trials ten behoeve van hoofdstuk 7 was afgesloten, werden de resultaten van tenminste 20 nieuwe trials gepubliceerd waarin de effectiviteit van de nieuwe cholesterolverlagende middelen (de statines) werd onderzocht (**hoofdstuk 7 update**). Vijf trials onderzochten met name klinische uitkomstmaten en 14 trials voornamelijk angiografische uitkomstmaten. Het effect van cholesterolverlaging lijkt nu aangetoond voor patiënten met CHZ. De recente bevinding dat cholesterolverlaging totale sterfte reduceert bij patiënten met CHZ is belangwekkend. De bewijsvoering is overtuigend voor de subgroep van blanke mannen van middelbare leeftijd, maar de toepasbaarheid van de resultaten naar de praktijksituatie van alledag is vooralsnog onduidelijk. Bovendien is er veel minder informatie en meer onzekerheid over de interpretatie van de geringere effecten van cholesterolverlaging bij personen zonder CHZ. Screening van het serumcholesterol lijkt het meest zinvol in patiënten met een hoog korte-termijn-risico voor CHZ sterfte, zoals post MI patiënten en mannen van middelbare leeftijd met meerdere risico factoren voor CHZ.

Ook de kosten-effectiviteit van cholesterolverlagende interventies werd geëvalueerd middels systematisch review van de literatuur (**hoofdstuk 8**). De resultaten van 38 economische evaluaties, gepubliceerd vóór 1997, werden beschreven, met speciale aandacht voor

de representativiteit van de populaties waarop de kostenmeting werd gebaseerd en de soorten kosten waarmee werd gerekend. De kosten van screening werden slechts in zeven studies meegewogen. Aanpassingen van de effectiviteit van de interventies voor de werkzaamheid in de praktijk van alledag werden zelden beschreven, immaterieële kosten werden nauwelijks meegewogen. Ongunstige bijwerkingen van cholesterol-screening of vermindering in effectiviteit in de werkelijkheid van alledag worden beschouwd, met problemen zoals misclassificatie van personen door meetfouten, labelling van personen als hypercholesterolaemische patiënten, of vermindering van kwaliteit van leven door dieettherapie. Kosten-effectiviteit ratio's varieerden van $0 tot meer dan een $1 miljoen per gewonnen levensjaar, en bleken zeer afhankelijk van geslacht en risicoprofiel van de patiënt, van de kosten van het cholesterol-verlagend middel, en van de soorten kosten die werden meegewogen in de berekeningen. Ondanks de grote variatie in uitkomsten bestond er een constante tendens naar een relatief gunstige kosten-effectiviteits ratio voor interventie in personen met CHZ vergeleken met personen zonder CHZ en voor mannen vergeleken met vrouwen.

In **hoofdstuk 9** staan de belangrijkste resultaten samengevat onder de topics 'inventarisatie van de huidige zorg', 'haalbaarheid van de richtlijnen' en de 'wetenschappelijke basis van de richtlijnen'. Methodologische overwegingen die nog niet aan de orde waren gesteld in de betreffende hoofdstukken worden bediscussieerd. De waarde van het onderzoeksmodel zoals gepresenteerd in hoofdstuk 1 wordt beschouwd, evenals het feit dat de predictieve waarde van serumcholesterol in relatie tot CHZ discussie blijft oprakelen. De impact van mogelijke methodologische zwakheden van de trial met het implementatie programma worden besproken, alsook de sterke en zwakke kanten van de literatuur-reviews. Mogelijke verklaringen voor het gebrek aan haalbaarheid van de cholesterol richtlijnen worden bediscussieerd. De generaliseerbaarheid van de effectiviteit van de cholesterolverlagende nieuwe middelen naar de werkelijkheid van alledag in de huisartsgeneeskunde blijft onduidelijk. Tenslotte worden aanbevelingen gegeven voor het updaten van de richtlijnen en voor implementatie strategieën met als belangrijkste aanbeveling dat de indicaties voor cholesterol-screening kunnen worden gereduceerd. Beperking tot patiënten met symptomen van coronaire hartziekten en patiënten met symptomen van familiaire hypercholesterolaemie lijkt geïndiceerd. De problemen in de uitvoerbaarheid van selectieve case finding en de ongunstige kosten-effectiviteits ratio's in ogenschouw nemende, lijkt terughoudendheid geboden in het screenen van personen zonder CHZ of familiare hypercholesterolaemie. De bruikbaarheid van risicotabellen waarmee individuen geclassificeerd kunnen worden aan de hand van hun cardiale risicoprofiel (bijvoorbeeld de Sheffield risicotabellen) verdient aandacht. Een geïntegreerde standaard voor preventie van coronaire hartziekte is vanuit wetenschappelijk oogpunt aanbevelingswaardig, en zal waarschijnlijk leiden tot een hogere compliantie dan de separate hypertensie en cholesterol richtlijnen zoals die nu bestaan. Tot slot worden nog enkele aanbevelingen gedaan voor verder onderzoek op dit terrein.

Dankwoord

Nadat ik mijn eerste beetjes werkervaring had opgedaan bij de vakgroepen Epidemiologie en Huisartsgeneeskunde, kwam er een telefoontje van Richard. "Voel je wat voor een implementatie-onderzoek?". Jasses, wat een modewoord, was het eerste wat me te binnen schoot. Richard, ik ben blij dat ik het avontuur ben aangegaan en kennis heb mogen maken met de rijke wereld achter dat modewoord, de wereld van quality assurance. Dat het implementatie-deel van het project gecombineerd kon worden met literatuurstudie maakte het compleet. André, het verkennen van de wereld van technology assessment onder jouw leiding was een plezier. Ik dank jullie voor de bezielde begeleiding waardoor dit project, waar quality assurance en technology assessment elkaar raken, kon uitgroeien tot dit proefschrift. Ik heb veel van jullie mogen leren.

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Curriculum Vitae

Trudy van der Weijden werd geboren op 8 april 1962 te Sint Michielsgestel. In 1980 werd het diploma gymnasium ß aan het Maurick-college te Vught behaald. Gedurende een jaar werkte zij als verpleegkundig-assistente in een revalidatiecentrum voor dubbelgehandicapte teenagers te Londen. Na de propaedeuse Gezondheidswetenschappen aan de Universiteit Maastricht (1981/82), werd gestart met de studie Geneeskunde aan dezelfde universiteit. In 1989 behaalde zij het arts-examen, waarna twee kortdurende aanstellingen volgden aan de Universiteit Maastricht. Namelijk als toegevoegd onderzoeker bij de vakgroep Epidemiologie en de vakgroep Huisartsgeneeskunde. Na een korte verkenning als sociaal verzekeringsarts bij de DGD Maastricht, was zij van begin 1991 tot medio 1994 aangesteld als toegevoegd onderzoeker bij de vakgroep Huisartsgeneeskunde voor het project waarvan dit proefschrift verslag doet. Sindsdien werkt zij bij deze vakgroep als onderzoeker, met research-taken voor de Werkgroep Onderzoek Kwaliteit (WOK), voor de vakgroep Medische Sociologie, voor de werkgroep Meta-analyse Diagnostisch Onderzoek (MEDI-ON), en met onderwijstaken voor het basiscurriculum Geneeskunde.